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# The American Journal of Medicine

VOL. II MAY, 1947 No. 5


## SYMPOSIUM ON STREPTOMYCIN




A timely and authoritative discussion of streptomycin, the most recent antibiotic to be made available for clinical use. The symposium is prefaced by Dr. Keefer's editorial appraising the results reported by the several contributors. A consideration of the general properties of streptomycin and relevant laboratory technics introduces the clinical reports on streptomycin by qualified and experienced observers in the fields of tuberculosis, bacterial endocarditis, tularemia, H. influenzae meningitis, urinary tract infections, peritonitis, wound infections and undulant fever. A current estimate of the toxic hazards of streptomycin concludes the discussion.

Dr. Keefer summarizes the symposium by stating that streptomycin is "extremely valuable and effective in controlling many infections that were uninfluenced by any other existing chemotherapeutic agent," and that its toxicity "is sufficiently low to justify the use of this drug in all serious or potentially serious infections due to penicillin-resistant, streptomycin-sensitive organisms."


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*Albrecht, F. K.: Modern Management in Clinical Medicine, Baltimore, The Williams and Wilkins Co., 1946, p. 170.

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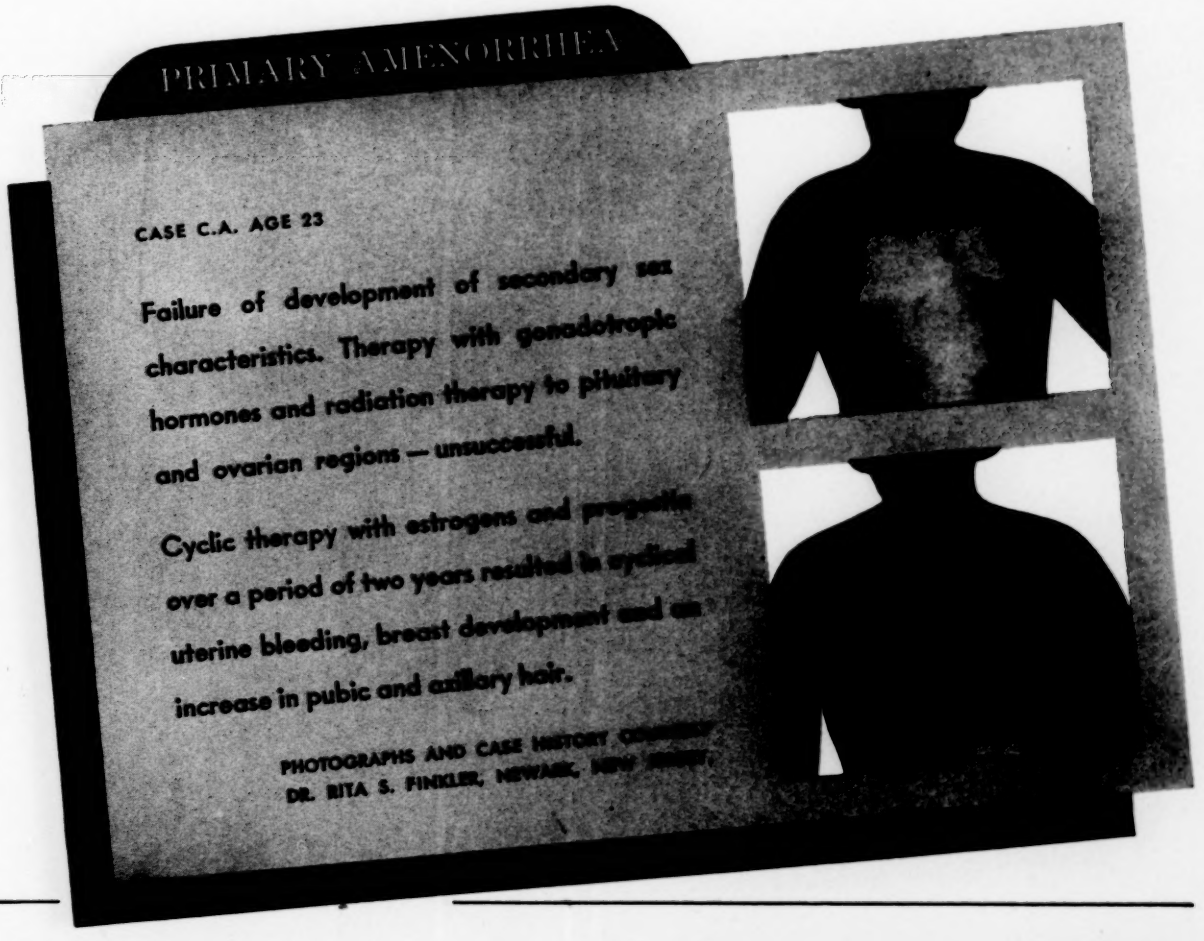


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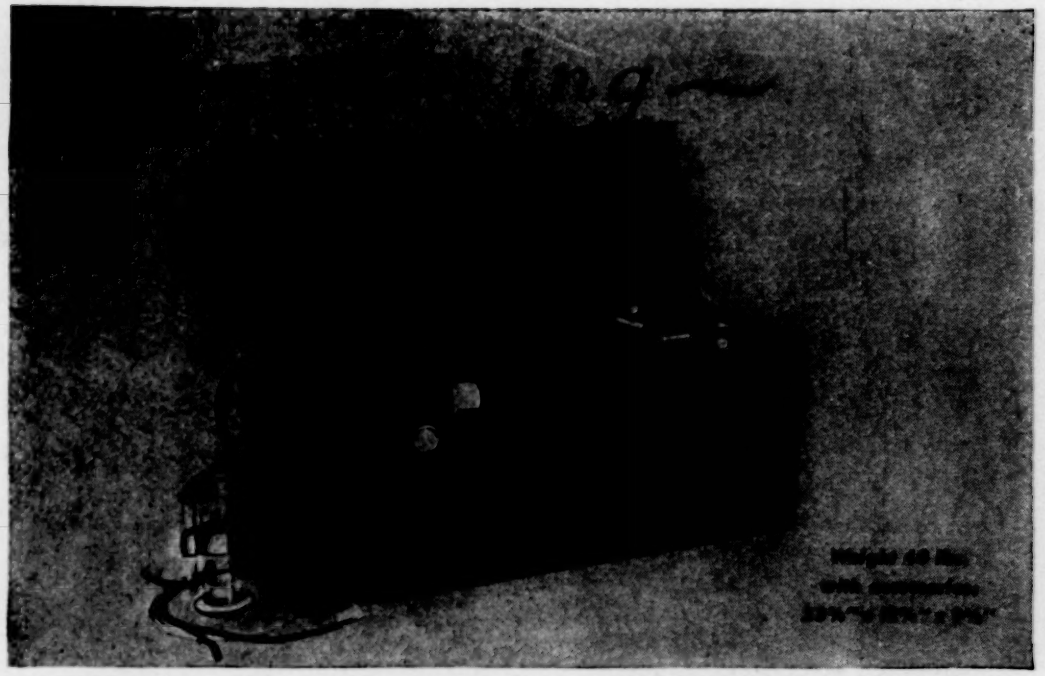

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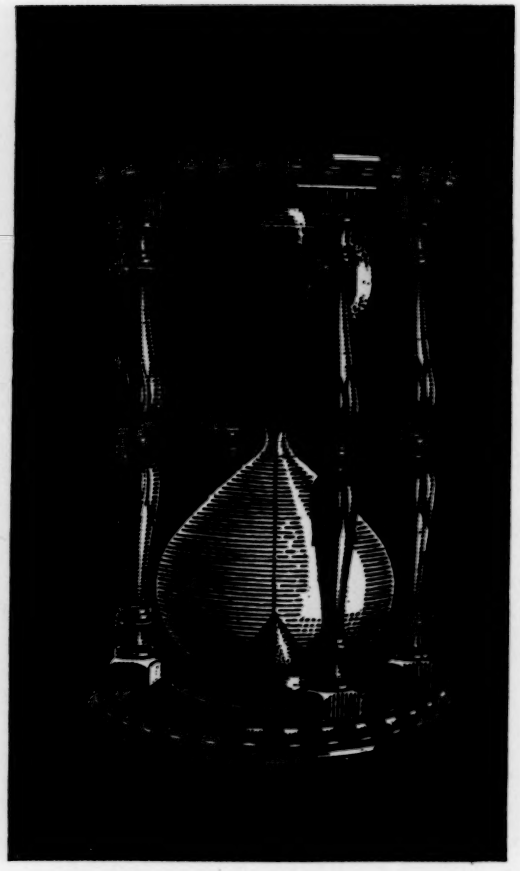

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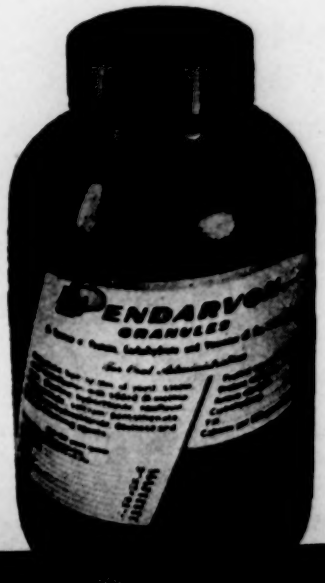

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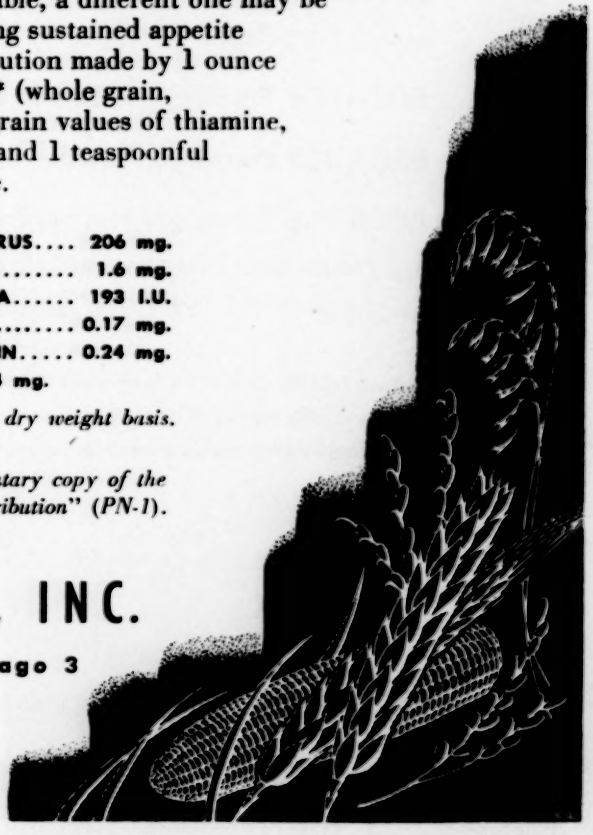

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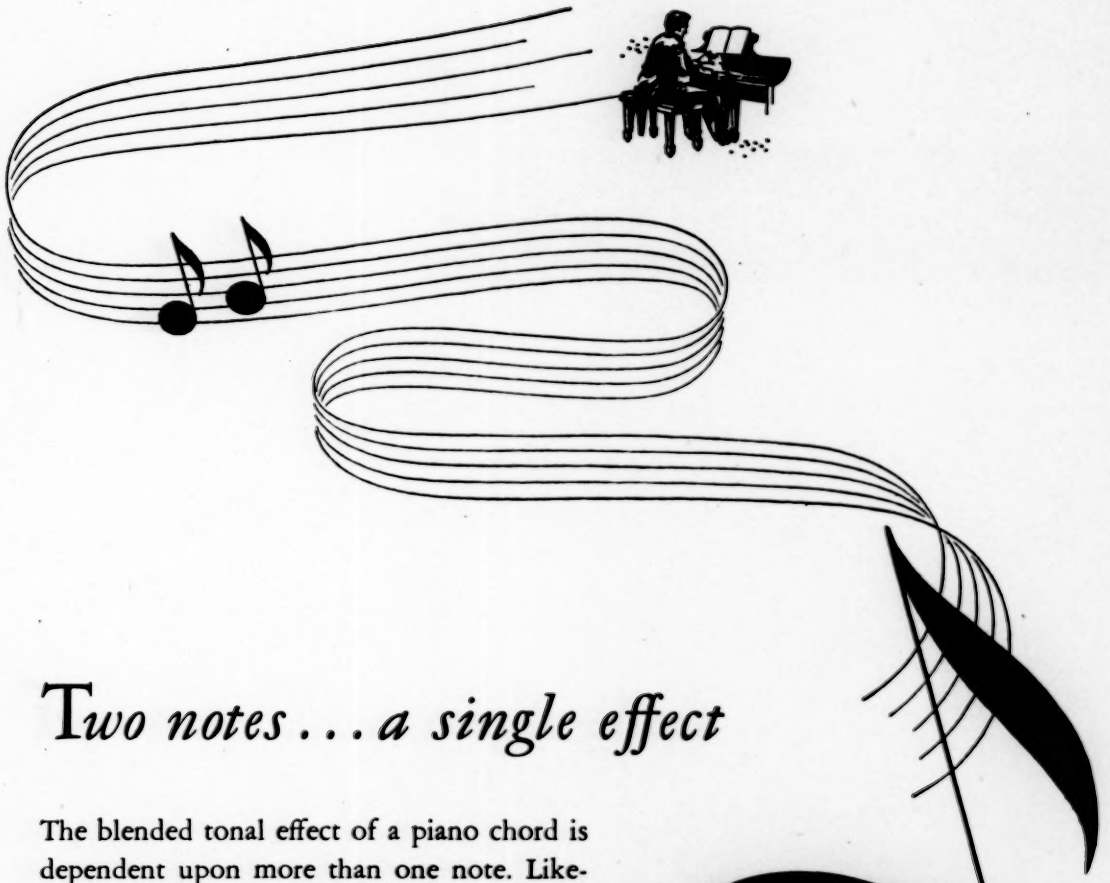

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The American Journal of Medicine

VOL. II MAY, 1947 No. 5

# Editorial

## Streptomycin

THERE is good evidence from the papers appearing in this symposium to support the statement that streptomycin is an extremely valuable antiinfective agent in the treatment of many infections that are resistant to either the sulfonamides or to penicillin. Thus, streptomycin has taken its place along with the sulfonamides and penicillin as a potent and valuable chemotherapeutic agent. Its effect in tularemia is unquestioned and in many cases dramatic. The results reported by Foshay are extremely impressive and carry great weight. The statement that "there is uniform agreement that streptomycin is an extremely effective therapeutic agent in tularemia" is supported by the data and by a wide experience with the treatment of this disease with other methods. It is noteworthy that highly satisfactory results can be obtained with a total dosage schedule of 2 to 3 Gm. given over a period of four to six days.

Dr. Alexander gives us precise information concerning the position of streptomycin in the treatment of H. influenzae meningitis. Her broad experience with the use of various methods of treatment in this disorder suggest that streptomycin should be used alone only in mild or moderately severe cases. The criteria for the use of various forms of combined therapy such as streptomycin alone, or sulfadiazine and antiserum, or the combined use of sulfadiazine with either streptomycin or Type B H. influenzae antiserum are spelled out very clearly in the paper.

That streptomycin has a small but definite place in the treatment of bacterial endocarditis is emphasized by Hunter. The patients with gram-negative bacillary infections who have an organism that is sensitive to streptomycin should all receive treatment. Also, those patients with penicillin-resistant, streptomycin-sensitive organisms that fall into the gram-positive group should be treated intensively.

The position of streptomycin in the treatment of urinary tract infections has been defined by Hewitt and for wounds and peritonitis by Howes and Zintel, respectively. All these studies demonstrate that streptomycin plays a definite part in controlling these complicated infections.

The review of the present status of streptomycin treatment in tuberculosis by Hinshaw, Pyle and Feldman serves to stress once again the importance of studying this infection further and with greater intensity. One cannot help but be impressed with the positive effects of chemotherapy in these various tuberculous infections. When the statement that "streptomycin is the most effective antibacterial agent known for tuberculosis" is combined with another, "experience with this antibiotic agent has proved that tuberculosis is a disease amenable to antibacterial therapy," there are good grounds for believing that great strides will be made in developing new methods for

treating one of the most important infections in man.

The results reported by Finch in acute brucellosis strongly suggest that the treatment of these patients should be carried out over a period of at least three to four weeks with 2 to 3 Gm. of streptomycin a day. It is a striking fact that in this disease, as well as in enteric infections due to E. typhosa and salmonella strains, the results of treatment with streptomycin have not been dramatic or impressive. It is far from clear why typhoid bacilli that are sensitive to streptomycin *in vitro* cannot be destroyed in the body when concentrations of the antibiotic are obtained in body fluids that are higher than is necessary to kill the organisms *in vitro*. It would be of great importance if we knew the mechanism of this phenomenon.

It has been pointed out that one of the limiting factors in using streptomycin is the rapid development of so-called bacterial resistance. The mechanism by which this resistance develops is not wholly understood. Perhaps one of the reasons for our lack of understanding of this phenomenon is that we are almost wholly ignorant of the mode of action of streptomycin on bacteria. It is not too much to expect that more information concerning the mode of action of streptomycin might assist one in understanding this problem of bacterial resistance and provide us with ways and means of preventing its development.

The toxic reactions as summarized by McDermott and the tests for bacterial sensitivity and methods of streptomycin determination in body fluids by Herrell and Heilman point to a number of the important practical features in the management of patients who are receiving streptomycin.

It seems plain from McDermott's studies that reactions from streptomycin follow the use of highly purified material as well as material containing not more than 50 to 60 per cent streptomycin. Also, it is clear that the larger the daily dose and the longer the treatment the higher the incidence of reactions. McDermott makes the point that toxicity cannot be considered apart from the diseases for which the drug is used. On a basis of his studies, it is stated that 3 Gm. a day represents the maximum limit of a safe dose. On the whole, however, it can be stated that the toxicity is sufficiently low to justify the use of this drug in all serious or potentially serious infections due to penicillin-resistant, streptomycin-sensitive organisms.

It can be said that streptomycin is another antibiotic agent that is extremely valuable and effective in controlling many infections that were uninfluenced by any other existing chemotherapeutic agent. Its discovery and application shows what can be accomplished in a group of extremely stubborn infections. It is to be hoped that our knowledge of its usefulness will be extended still further in the future.

CHESTER S. KEEFER, M.D.

# Streptomycin

## *General Considerations, Tests for Bacterial Sensitivity and Methods of Measurement of Streptomycin in Body Fluids*

WALLACE E. HERRELL, M.D.* *and* FORDYCE R. HEILMAN, M.D.*

ROCHESTER, MINNESOTA

THE antibiotic agent, streptomycin, was first described by Schatz, Bugie and Waksman[1] in January, 1944. The substance was produced by an actinomycete which had been discovered and described some years previously by Waksman. This actinomycete was subsequently placed in the genus Streptomyces by Waksman and Henrici[2] and is now known as "Streptomyces griseus." The newly discovered antibiotic was consequently given the name "streptomycin." Schatz, Bugie and Waksman suggested that this antibacterial agent possessed properties which might make it useful in the treatment of disease caused by certain gram-negative as well as some gram-positive pathogens.

Streptomycin behaves chemically as an organic base. It is rather thermostabile. It is not soluble in ether or chloroform but it is soluble in water and dilute acids. It was evident from the original reports that in the group of organisms which might be inhibited by the action of streptomycin were such microbes as Escherichia coli, Bacillus subtilis, Aerobacter aerogenes, Proteus vulgaris and some species of Salmonella. Likewise, it appeared that streptomycin possessed a limited suppressive effect on Pseudomonas aeruginosa.

That Mycobacterium tuberculosis was sensitive to the action of streptomycin *in vitro* was suggested by the reports by Waksman, Bugie and Schatz[3] and by Schatz and Waksman.[4] That streptomycin exerted an inhibitory effect on Mycobacterium tuberculosis *in vivo* was first reported by Feldman and Hinshaw.[5] These and other studies led to a rather intensive experimental and clinical trial of streptomycin in the treatment of tuberculosis. The results of such studies will be discussed in other articles in the present symposium.

Further studies by the investigators at Rutgers University[6] revealed that streptomycin was effective in the treatment of certain experimental infections owing to Salmonella schottmülleri, Pseudomonas aeruginosa, fowl typhoid and Brucella abortus. Unfortunately, subsequent clinical trials have not proved streptomycin to be of outstanding value in the treatment of clinical infections due to the organisms just mentioned.

It was evident from the *in vitro* and *in vivo* studies reported by one of us (Heilman)[7,8] that streptomycin possessed therapeutic possibilities in the treatment of infections due to Pasteurella tularensis (tularemia) and infections due to organisms of the Friedländer group (Klebsiella). From studies carried out at the Mayo Clinic[9] and elsewhere[10] it was evident that streptomycin possessed antibacterial activity against Hemophilus influenzae. The studies reported by Hegarty, Thiele and Verwey[11] indicated likewise that streptomycin possessed value in the treatment of experimental infections owing to Hemophilus pertussis. While streptomycin has been used satisfactorily in the treatment of clinical cases of infection

* From the Division of Medicine and the Section on Bacteriology, Mayo Clinic, Rochester, Minn.

due to Hemophilus influenzae, studies on its possible use in pertussis have not been reported at the time of this writing.

Streptomycin has been found to inhibit the growth *in vitro* of a great number of microbes. In this article we are concerned only with those organisms which are considered pathogenic for man. The organisms which at present may be considered for practical purposes to be sensitive and which are pathogenic for man are listed in Table 1. It should be emphasized, however, that

TABLE 1
ANTIBACTERIAL ACTION OF STREPTOMYCIN

| Organisms Sensitive to Streptomycin |
|---|
| Escherichia coli |
| Eberthella typhosa |
| Salmonella paratyphi (some strains) |
| Salmonella enteritidis (some strains) |
| Shigella dysenteriae |
| Proteus vulgaris |
| Aerobacter aerogenes |
| Pseudomonas aeruginosa (Bacillus pyocyaneus) |
| Klebsiella pneumoniae |
| Hemophilus influenzae |
| Hemophilus pertussis |
| Staphylococcus aureus (some strains) |
| Mycobacterium tuberculosis |
| Brucella melitensis |
| Brucella abortus |
| Brucella suis |
| Pasteurella tularensis |
| Pasteurella pestis |

the sensitivity of these organisms varies greatly. It should be emphasized further that the inclusion of an organism in this list does not mean that streptomycin has proved effective in the treatment of clinical infections due to that organism. For the purpose of the discussion the organisms might well be listed in two groups: (1) those that are rather highly sensitive and (2) those that are moderately sensitive. In the group of organisms which could be considered rather highly sensitive are placed Pasteurella tularensis, Pasteurella pestis, Hemophilus influenzae, Hemophilus pertussis, Klebsiella pneumoniae, Escherichia coli, Aerobacter aerogenes, Proteus vulgaris and Mycobacterium tuberculosis. The organisms which could be considered only moderately sensitive are Eberthella typhosa, Salmonella paratyphi (some strains), Salmonella enteritidis (some strains), Shigella dysenteriae, Pseudomonas aeruginosa (Bacillus pyocyaneus), Staphylococcus aureus (some strains), Brucella melitensis, Brucella abortus and Brucella suis.

With certain exceptions, the sensitivity of organisms to streptomycin as determined by *in vitro* studies can be used as an index of the probable effectiveness of the antibiotic in treatment of clinical infections. It was evident from even the earliest experimental studies that the variation in sensitivity of different strains of the same organisms to the action of streptomycin was of considerable importance from a therapeutic point of view. Different strains of the same bacterial species may vary markedly in their sensitivity to streptomycin. This immediately suggests the importance of testing the sensitivity of the strain isolated from the patient before and during treatment. This necessitates a close collaboration between the clinician and the laboratory worker in the management of patients suffering from infections in which streptomycin may be used as a therapeutic agent.

Two other important considerations should be mentioned in connection with the therapeutic use of streptomycin. One is the definite variation in the absorption and excretion of streptomycin by different patients or by the same patient at different times. This variation may make the clinical evaluation of the antibiotic agent difficult at times. Second, but of no less importance, is the ability of certain pathogens to develop resistance to streptomycin. Some strains and species of organisms may develop resistance to streptomycin with incredible rapidity. This has been demonstrated repeatedly both *in vitro* and *in vivo*. This observation is exceedingly important from a clinical standpoint. Buggs and his associates[12] have pointed out, however, the difficulties which may be encountered in

studying this problem clinically. It is difficult at times to determine whether or not the same organism is being isolated at different times from a given patient. Moreover, organisms may develop resistance *in vitro* but will not necessarily develop resistance in the body. From a clinical standpoint it is important to remember that organisms which easily can be made resistant to streptomycin *in vitro* at times may retain their sensitivity in patients although the patient has received repeated courses of streptomycin.

All of the previously mentioned facts emphasize the importance of adequate laboratory methods of assay and adequate methods for testing bacterial sensitivity which will be discussed later in this paper. Furthermore, because of the reasons previously stated, certain dictums have been adopted in the clinical use of streptomycin. Because of the development of resistance, it is essential that bacteria be eradicated as completely as possible in the shortest possible time if good clinical results are to be obtained. This rule implies the administration of large doses of streptomycin from the onset of treatment. It also calls for frequent recourse to the laboratory for determination of the sensitivity of the organism especially if the infection is not responding satisfactorily to treatment. The removal of foreign bodies and the eradication of foci by surgical means before or soon after treatment is begun is important. The presence of foreign bodies or foci favors the continuation of infection and thereby favors the possibility of the development of resistance on the part of the infecting organism. In the treatment of infections in which stasis and obstruction play a rôle, such as in infections of the urinary tract, it is important that these two factors be eliminated. Since it is known that streptomycin exerts its maximal antibacterial effect in the presence of an alkaline medium, it is suggested that the urine should be kept alkaline.

Much has been learned concerning the absorption, diffusion and excretion of streptomycin. It was evident from the reports made by various investigators[13–20] that streptomycin, following its intramuscular or intravenous injection, diffuses rather readily into most body tissues. Following oral administration, streptomycin cannot be detected in significant amounts in the blood stream. On the other hand, the antibiotic is not destroyed in the gastrointestinal tract and large portions of the material administered orally can be recovered from the feces. It exerts an antibacterial effect on the intestinal flora and this observation suggests its use when a reduction in the bacterial content of the bowel is desired.

Satisfactory therapeutic concentrations of streptomycin will appear in the blood and urine following intermittent intravenous, intramuscular or subcutaneous administration. Approximately 60 to 80 per cent of streptomycin injected is excreted by the kidneys and may be recovered in the urine. It should be pointed out, however, that streptomycin at times may accumulate to toxic levels in the blood stream of patients who have poor renal function. Streptomycin appears to diffuse into the peritoneal cavity in substantial amounts in the presence of early peritonitis. Streptomycin does not diffuse readily into the cerebrospinal fluid of normal individuals; however, therapeutic amounts appear to diffuse readily into the spinal fluid in the presence of meningitis. Streptomycin diffuses into the tissues of the eye and also appears to diffuse through the placenta and thereby reaches the fetal circulation. It does not appear to diffuse readily into empyema cavities. Streptomycin appears to be excreted in the bile. When streptomycin is introduced into the tracheobronchial tree by means of nebulization, it is not absorbed into the blood stream in significant amounts.

When streptomycin was first introduced, the unit of potency was defined on the basis of its antibacterial activity. The unit of potency was based on that amount of the material required to inhibit the growth of a given strain of Escherichia coli. It was known as the "S" unit of Waksman. Recently, the metric system has been adopted in connection with dosage of streptomycin. One microgram of pure streptomycin is approximately equivalent to 1 S unit; 1 mg. to approximately 1,000 S units and 1 Gm. to 1,000,000 S units. Experience at present indicates that the minimal daily dose of streptomycin should be 1 to 3 Gm. (1,000,000 to 3,000,000 S units). In the treatment of overwhelming infection, as much as 5 Gm. per day may be given. For intermittent intravenous or intramuscular injections, the total daily dose is dissolved in 16 cc. of physiologic saline solution or distilled water. An average of 2 cc. of this solution is injected every three hours. In some instances, satisfactory results may be obtained by making larger injections at intervals of four or six hours. The recommended daily dose of streptomycin for oral administration is 2 to 4 Gm. in four divided doses. For intrathecal administration of streptomycin it is recommended that 100 mg. of streptomycin be dissolved in 5 or 10 cc. of physiologic saline solution. This quantity may be administered every twenty-four to forty-eight hours. For nebulization, the concentration recommended is, as a rule, 50 mg. per cc. of physiologic saline solution. For local application, concentrations of the drug which have been used vary from 10 to 100 mg. per cc.

## CLINICAL TRIALS

In recent years streptomycin has been subjected to rather extensive clinical trials by a host of investigators. These trials have been limited, for the most part, to tuberculosis, bacteremia and subacute bacterial endocarditis, peritonitis, influenzal meningitis, tularemia, infections of the urinary tract and undulant fever. Streptomycin also has been used locally in the treatment of wounds infected with organisms known to be sensitive to its action. A detailed discussion of these results will be dealt with in separate articles in this symposium. Some clinical experiences in the use of streptomycin in a variety of bacterial infections treated at the Mayo Clinic have been reported elsewhere.[21–25]

## TESTS FOR SENSITIVITY OF BACTERIA TO THE GROWTH-INHIBITING EFFECT OF STREPTOMYCIN

The activity of streptomycin in a bacteriologic medium is affected by the pH and by the presence of cysteine, sodium thioglycollate and other reducing substances.[3,26–28] In a medium highly favorable to bacterial growth more streptomycin may be required to inhibit growth of a given strain of bacteria than in a medium of deficient nutritional value.[29,30] Since streptomycin becomes less active if the substrate is acid or is in a reduced state, tests of sensitivity should be carried out in mediums containing no fermentable sugar and adjusted to a pH close to neutrality, and under aerobic conditions.

There are several methods of testing the sensitivity of bacteria to streptomycin. In one of these the test is carried out in a series of tubes, containing liquid medium suitable for growth of the organism, to which various amounts of the antibiotic[12] have been added. The liquid medium in the tubes is inoculated with a drop of a dilute suspension in broth of the organism and incubated for eighteen hours or until good growth appears in the control tube. The lowest concentration of streptomycin which completely inhibits growth is recorded. Since the end point of growth may be difficult to determine by inspection, a loopful of material from each

of the tubes near the end point may be streaked on an agar plate to determine in which tubes growth has or has not occurred. Prolonged incubation may allow the development of resistant forms and alter the end point. The larger the primary bacterial inoculum the greater the chance that it will contain some of the more resistant organisms which are usually present in any culture.

Because of the difficulty in determining the end point of growth in liquid mediums, in our laboratory tests for sensitivity to streptomycin are carried out routinely by streaking a dilute suspension of the organism on agar plates containing various amounts of streptomycin. The plates are prepared from nutrient agar adjusted to pH 7.2 to 7.4. Blood agar is used for more fastidious organisms. Seven plates are prepared in which have been incorporated by careful mixing, previous to solidification of the agar, 50, 25, 12.5, 6.25, 3.12, 1.56 and 0 units (micrograms) of streptomycin per cc., respectively. In order that several different strains of bacteria may be tested on one set of plates, each plate is divided into several sectors by marking on the back with a pencil used for marking glass. The sectors on each plate are numbered. Dilute suspensions in nutrient broth (which contains no sugar) of the organisms to be tested are prepared and a loopful of each suspension is streaked on each plate over the sector assigned to that suspension. A suspension of a stock strain of staphylococci of known sensitivity is always streaked on one of the sectors of each plate. The use of this stock strain is a test of the proper preparation of the plates and is of importance since the decision as to whether or not a patient is to be treated with streptomycin often rests on the results of this test of sensitivity. The inoculated plates are incubated at 37°c. overnight or until there is good growth of the test strain on the control plate containing no streptomycin. The lowest concentration of streptomycin which completely inhibits growth of each strain then is recorded.

If the plate method is used, difficulty may be encountered in testing the sensitivity to streptomycin of freshly isolated strains of Brucella abortus which require an increased tension of carbon dioxide. Placing the plates in an atmosphere of 10 per cent carbon dioxide lessens the activity of streptomycin in the test plates, presumably by lowering the pH of the medium. After several subcultures, the carbon dioxide requirements of such strains are decreased sometimes. The organism then will grow in an atmosphere of 2 to 3 per cent carbon dioxide which concentration will not alter the pH of medium significantly and, therefore, will not alter the results of the test of sensitivity to streptomycin.

The standard solution of streptomycin used in making the dilutions for the preparation of the test plates is stable and may be kept in a refrigerator in a sterile corked tube for several weeks without significant loss of titer.

Simpler methods, giving less accurate measurements of the degree of sensitivity of an organism to streptomycin, are available. Plates seeded with the organism on which are placed cups filled with solutions containing various concentrations of streptomycin or disks of blotting paper (obtainable from Schleicher and Schuell, New York) dipped in such solutions may be prepared.[31] After incubation, inhibition of growth around the cups or disks is noted and compared with similar preparations on plates seeded with an organism of known sensitivity. Another method consists in dipping a disk of blotting paper in a solution containing 20 units of streptomycin per cc. and placing it on a plate of nutrient agar. Organisms to be tested are streaked outward from the periphery of the paper disk and the distance from the disk that growth is in-

hibited after incubation is an index of sensitivity.

### MEASUREMENT OF STREPTOMYCIN IN BODY FLUIDS

Streptomycin in serum, urine or other body fluids is often measured by noting the volume of such material which must be added to a liquid bacteriologic medium to inhibit the growth of a test organism. It also frequently is measured by making various dilutions of the serum, placing these dilutions in cups on an agar medium inoculated with a test organism and after incubation measuring the zone of inhibition of growth around the cups.

Methods of making the test by adding various amounts of the serum or other fluid to be tested to liquid mediums containing the test organism have been described.[15,32,33] Such methods are somewhat more sensitive than the cup-plate method and simpler to perform. Their disadvantages are that the body fluid to be tested must be sterile; the end point of growth in liquid mediums is often difficult to determine; different amounts of body fluid may have different growth promoting properties for the test organism, and end points between the dilution intervals used cannot be detected.

In our laboratory, a method of using cups on agar plates which is similar in principle to that described by Stebbins and Robinson[34] is favored. This method does not accurately measure concentrations of streptomycin of less than 1 unit per cc. but since weaker concentrations are of doubtful therapeutic effectiveness, the method is sufficiently sensitive for general use. The test organism is a strain of Staphylococcus aureus which on agar gives relatively sharp margins at the edges of the zones of inhibition.

The test organism is maintained in nutrient broth by daily transfer. Since growth of the organism for prolonged periods on broth has yielded variants which have lessened the sharpness of the edges of zones of inhibition around the cups, the series of cultures in broth is discarded at the end of a week and a new series is started from a stock agar slant culture which is preserved in the refrigerator.

The test is carried out in a system adjusted to pH 8. This pH is chosen because streptomycin is more active at pH 8 than at neutrality. All dilutions in the test are made in a sterile tenth-molar pH 8 buffer, prepared from potassium phosphate ($KH_2PO_4$ and $K_2HPO_4$). Nutrient agar adjusted to pH 8 is used as the test medium. A commercial dehydrated medium with the pH already adjusted and known as "Streptomycin Assay Agar" (Difco) is satisfactory for the purpose. To furnish a perfectly flat surface for the test 12 cc. of unseeded melted agar is placed in each of a series of Petri dishes and allowed to harden. A second portion of melted agar is cooled carefully in warm water to 44° to 45°c. and inoculated with a broth culture of staphylococci which has been incubated for six hours. One cc. of a 1 in 100 dilution of this broth culture in a buffer solution is used for each 9 cc. of agar. A final dilution of $10^{-3}$ of the staphylococcal culture is obtained. The inoculated agar is agitated to distribute the organisms evenly. With a warm, widemouthed pipette 5 cc. of the seeded agar is distributed over the surface of the first layer of agar on each plate while the plate is rotated so that the seeded agar forms an even layer.

Sterile beveled porcelain or glass cylinders, such as are used in the assay of penicillin (sold under the trade name of penicylinders), are warmed slightly in a flame and placed on the surface of the hardened agar. These cylinders should be just warm enough to seal the beveled surface in the agar. Four or five sterile cylinders are placed on each plate. Four or more serial 1:1 dilutions in buffer of the samples of body fluids for assay are prepared, the

number of dilutions depending on the expected concentration of streptomycin. For the standard, dilutions of streptomycin in buffer are prepared which contain 1, 2, 3 and 4 units per cc., respectively. Each of the dilutions of the test sample and standard is placed in a separate cup with a capillary pipette; each cup is nearly filled. Duplicate tests are set up on a separate set of plates for all of the samples as well as the standard. The Petri dishes are covered with unglazed porcelain tops to prevent dripping from condensed water and placed in the refrigerator overnight to allow the material to diffuse from the cups into the agar. Following this the plates are incubated for twenty-four hours at 30°c. Then the cups are removed from the plates and the diameter of the zones of inhibition of growth of the staphylococci is estimated to the nearest 0.2 mm., preferably by means of a colony counter equipped with a glass plate ruled 10 lines to the centimeter. Such ruled glass plates are available from commercial sources.

The diameters of the zones from duplicate cups are averaged. A curve is drawn on arithmetic graph paper by plotting the diameter of the zones of inhibition of the cups containing the standard streptomycin solutions on the ordinate against the concentrations in units of streptomycin per cc. of fluid on the abscissa. For a model, one of several references may be consulted.[35–37] From the standard curve the concentration of the drug in the sample under test can be read by noting the concentration of streptomycin on the abscissa of the standard curve which corresponds on the ordinate to the diameter of the zone of inhibition around the samples. This reading should be multiplied by the dilution of the body fluid used in the cups. If sizes of the zones of two different dilutions of the sample fall within the range of the standard curve, the concentration of each dilution is calculated and the results are averaged to give the concentration in the body fluid.

Specimens contaminated with bacteria may be assayed by this method. Two cc. of a sample is required for an assay. With assays of urine, if it is desired to hurry the test, the plates may be placed directly in the incubator without preliminary storage in the refrigerator since urine diffuses rapidly from the cups. Samples of the original specimen being assayed should be preserved in the cold in case the assay has to be repeated at higher dilutions. Disks of blotting paper dipped in the test fluid or measured drops of test fluid placed directly on the seeded agar are used in place of cups by some workers.[36,37]

If only an estimate of the amount of streptomycin is desired, the test may be simplified. Several cups placed on a plate of seeded agar are filled with various dilutions in saline solution of the sample to be tested and the plates are incubated at 30° or 37°c. overnight. The extent of the zones of inhibition is a rough measure of the concentration of streptomycin.

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# Streptomycin in Tuberculosis*

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Although attempts to attack tuberculosis by chemotherapeutic means are as old as our knowledge of the disease, it was not until 1940 that a substance was found capable of arresting tuberculosis *in vivo*. In that year Feldman, Hinshaw and Moses[1] reported that promin (sodium p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate) had a striking effect on tuberculosis induced in guinea pigs. A few other drugs of the sulfone series were found to have a similar suppressive effect on experimental tuberculosis, and attempts to use these drugs clinically followed.[2] The results were suggestive but never fully convincing, possibly because the sulfone compounds were found to be too toxic to permit adequate treatment of tuberculosis of human beings.

From the first, streptomycin gave great promise as an agent capable of suppressing tuberculosis. In their early reports Schatz and Waksman[3] noted that a human strain of Mycobacterium tuberculosis was sensitive to streptomycin *in vitro*. Investigations of this antibiotic agent were begun in April, 1944, at the Mayo Foundation with the methods previously developed for chemotherapeutic testing in experimental tuberculosis.[4] These investigations proved conclusively that streptomycin consistently would arrest and at times even apparently eradicate well established tuberculosis in the highly susceptible guinea pig.[5,6]

In the most severely controlled of the experiments, forty-nine guinea pigs were infected with a virulent standard human strain of tubercle bacilli. Forty-two days later results of tuberculin tests of all the animals were positive. On the forty-eighth day of infection biopsy of the liver was performed in each case and histologic evidence of the disease was obtained. On the forty-ninth day after infection twenty-five of the animals were treated with streptomycin. Treatment was continued for a total of 166 days. Approximately 70 per cent of the control animals succumbed to infection within this period, whereas only 8 per cent of the animals treated died before the experiment was terminated 215 days after infection.

At necropsy all control animals showed evidence of severe, widely disseminated tuberculosis. In marked contrast, the treated animals showed little or no gross or microscopic evidence of infection. In a majority of animals, treatment with streptomycin must have had a suppressive rather than a sterilizing effect on the infection, because tubercle bacilli were recovered by animal inoculation tests from the spleens of fifteen of the twenty-five treated animals. However, in nine of the treated animals the sensitivity to tuberculin was reversed from positive to negative, and in only two of this group were tubercle bacilli recovered from the spleens by animal inoculation. Streptomycin was tolerated well by the test animals, and there was no histologic evidence of drug toxicity in any of the organs. Youmans and McCarter[7] reported equally encouraging results from the treatment with strepto-

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mycin of mice infected experimentally with tuberculosis.

### CLINICAL USE OF STREPTOMYCIN*

The clinical use of streptomycin for tuberculosis was begun in December, 1944. In the last two years streptomycin has been used by our colleagues and us in more than 100 cases of tuberculosis of various types. A preliminary report of the earlier work was given in September, 1945,[8] and more recently a more comprehensive account was published in collaboration with Dr. Karl H. Pfuetze.[9] At present approximately 200 additional patients are being treated with streptomycin at selected institutions, under the auspices of the American Trudeau Society. In addition, a large number of patients are receiving streptomycin for tuberculosis in other institutions. When the mass of data from all this investigation is assembled, perhaps within a few months, it should be possible to make a more accurate appraisal of the drug, not only in regard to its therapeutic efficacy in tuberculosis, but also as to its toxicity and such factors as the effective dosage and optimal duration of treatment.

In all discussions of the therapeutic possibilities of streptomycin in tuberculosis, we must view the situation in proper perspective. The ability of streptomycin to suppress the disease is unique and at times apparently remarkable. The limitations of streptomycin are just as real. Because of certain toxic potentialities, its inadequacy in some clinical situations, and the expense of prolonged periods of treatment, the indiscriminate use of streptomycin in the treatment of tuberculosis must be discouraged.

* The streptomycin used in these studies was supplied by Merck & Co., Inc., Abbott Laboratories, and The Upjohn Company. From March 1 to September 1, 1946, all supplies were allocated through the Committee on Chemotherapeutics and Other Agents of the National Research Council, Dr. Chester S. Keefer, Chairman. Since September, 1946, material has been supplied by the Committee on Therapy of the American Trudeau Society.

Among the indications for the use of streptomycin in tuberculosis are all forms of hematogenic disease, including generalized miliary tuberculosis and meningitis, the prognosis of which has hitherto been regarded as hopeless. Of twelve patients who had disease of this type and were treated with streptomycin at the Mayo Clinic, four are still living and have been observed for periods of from six to twelve months. Treatment of each of these four patients has been discontinued for from four to six months, and there is not any evidence of reactivation of the disease. Three of these patients who originally presented the classic picture of tuberculous meningitis, are ambulatory and free of symptoms, although two of them have residual neurologic disturbances. One of these two has marked nerve deafness which may be a toxic effect of streptomycin. The other patient has symptoms of cerebellar dysfunction, which are thought to be sequelae of the meningitis.

In treating tuberculous meningitis it is imperative that streptomycin be given both parenterally and intrathecally and as early in the course of the disease as possible. The first five patients who were given streptomycin for tuberculous meningitis at the Mayo Clinic received it parenterally only. Although four of them improved temporarily, all eventually died.[10] It is suggested that the drug be given by lumbar or cisternal puncture, in amounts of from 100 to 200 mg. every twenty-four to forty-eight hours for from four to seven weeks or longer. A single dose of streptomycin is dissolved in 8 to 10 ml. of physiologic saline solution and injected after the withdrawal of 10 to 15 ml. of spinal fluid. In addition, streptomycin probably should be given parenterally for a long period. The four patients with tuberculous meningitis who survived received an average dose of 2 Gm. a day by parenteral administration for an uninterrupted period of six months.

The patient who has early tuberculous meningitis usually improves in all respects within one to three weeks after treatment with streptomycin is begun. In our more successful cases it has been impossible to demonstrate tubercle bacilli in the spinal fluid, either by culture or inoculation of guinea pigs, after six to eight weeks of treatment, although their presence was demonstrated prior to treatment in each case. There is a tendency for the spinal fluid to remain somewhat abnormal; for example, the cell count and the concentration of protein are usually higher than normal.

Generalized miliary tuberculosis, likewise, should be treated vigorously; the patient should receive 2 to 3 Gm. of streptomycin daily by parenteral administration for several months. Striking, often almost complete clearing of the pulmonary lesion is noted in the roentgenograms within a month or two, but if actual healing is to occur, treatment must be prolonged. One patient in our group who had generalized miliary tuberculosis without meningitis received 2.4 Gm. of streptomycin a day for a period of four months. His disease has remained in a state of clinical remission for three months since cessation of treatment. Treatment in three similar but more advanced cases of miliary tuberculosis resulted in temporary improvement only.

In addition to pulmonary lesions of hematogenic origin, pulmonary tuberculosis suitable for treatment with streptomycin includes recent lesions of bronchiogenic dissemination, exudative lesions, and in general all recent but rapidly progressive tuberculosis which is not likely to be brought under control by the usual methods of treatment. Pulmonary tuberculosis has been treated satisfactorily by average daily doses of from 1 to 3 Gm., administered parenterally, for a total period of from two to six months. Clinical improvement, including decrease in fever, increase in appetite and reduction in cough and expectoration, is noted early, often within a week or two after administration of streptomycin is begun. Improvement usually can be demonstrated roentgenographically within one to two months. Although closure of pulmonary cavities has been observed roentgenographically during the period of treatment with streptomycin or in the ensuing months, cavities more frequently remain patent, especially if they are thick walled. Likewise the findings in the sputum are changed from positive to negative in only approximately 50 per cent of cases of far advanced pulmonary tuberculosis with extensive cavitation.

In our experience the patient whose pulmonary tuberculosis has improved during treatment with streptomycin usually continues to improve after this treatment is discontinued. In only a few cases of pulmonary tuberculosis has reactivation or extension of the disease occurred after cessation of treatment. If the tubercle bacilli recovered from the sputum of these patients are still sensitive to streptomycin *in vitro*, it is likely that the patient will respond to further treatment with the drug. If the strain has become resistant, there is less likelihood of repeating the earlier therapeutic result; but in some instances it has appeared that the resistant strains of bacilli were in the sputum and clinically sensitive strains were in the recurrent lesions.

Use of streptomycin in pulmonary tuberculosis possibly is indicated in conjunction with surgical procedures, such as lobectomy, pneumonectomy and even thoracoplasty. It is hoped that a preoperative course of the drug for one to three weeks and a postoperative course for two to four weeks will improve the patient's condition for operation and decrease the incidence of complications, such as the recrudescence of foci, extension of the disease to new regions and the development of tuberculous empyema. It is reasonable to believe that streptomycin

may make surgical intervention feasible more frequently in the treatment of tuberculosis.

A category in which streptomycin has been used with notable success includes tuberculosis of the hypopharynx, larynx and tracheobronchial tree. In our series of ten cases of tuberculosis in these sites lesions have healed promptly and have shown no tendency to recurrence for as long as twenty months after completion of treatment. For these ulcerating lesions of the respiratory tract we have given streptomycin both parenterally and by means of nebulization. For nebulization 500 mg. of streptomycin is dissolved in 20 ml. of physiologic saline solution and the patient is instructed to nebulize 2 ml. every hour for ten hours of the day. Repeated bronchoscopic examinations usually have revealed that healing was beginning within two weeks after treatment was started, and often healing was complete within four weeks. Treatment should probably be continued for seven or eight weeks or longer. It has not yet been determined whether either nebulization of streptomycin or its parenteral administration would be sufficient without the other method of treatment.

In our experience tuberculous draining sinuses have responded well to treatment with streptomycin, even those of long duration which were refractory to all other methods of treatment. These include fistulous tracts due to tuberculosis of the chest wall, abdominal wall and scrotum, and to tuberculous lymphadenitis. We have learned that to prevent recurrence of these conditions it is necessary to continue treatment for several weeks after drainage has ceased, with superficial healing. Streptomycin is given parenterally, and adequate treatment apparently consists of about 2 Gm. a day for three or four months.

Other forms of tuberculosis in which encouraging results have been obtained with streptomycin therapy in small series of cases include tuberculosis of the alimentary tract and peritoneum and tuberculosis of bones and joints. Results have been excellent in one case of previously intractable lupus vulgaris. In some other cases presumed to be cutaneous tuberculosis, improvement from treatment with streptomycin has been temporary or questionable.

Streptomycin has been somewhat disappointing in the treatment of some cases of tuberculosis of the genitourinary tract. As has been reported previously,[11] marked symptomatic improvement occurs in more than 50 per cent of such cases and the degree of tuberculous bacilluria usually is reduced sharply. In fact in several cases in which we and the urologists at the clinic collaborated in the treatment, the urine became free of Mycobacterium tuberculosis, as proved by culture and inoculation of guinea pigs. However, the tendency of tuberculous lesions in the kidney of human beings not to heal is well known and, therefore, the benefits of antibacterial treatment are often only temporary. After weeks or months of treatment or at varying intervals after treatment is discontinued, the tuberculous bacilluria is likely to return. The strain of tubercle bacilli is then usually resistant to streptomycin *in vitro*. It may be worthy of note that some patients continue to have amelioration of their symptoms, even after a resistant strain of Mycobacterium tuberculosis appears in the urine. Because of the palliative effect, the possibility of arresting the disease in a small proportion of cases, and the inadequacy of other therapeutic measures, streptomycin is certainly worthy of trial in some cases of bilateral renal tuberculosis and in tuberculosis of a solitary kidney. We do not regard it as a substitute for surgical procedures in cases of unilateral renal tuberculosis, although it may yet prove to be of value in the preoperative and postoperative treatment.

Among tuberculous conditions in which streptomycin is not indicated or in which the indication is less definite, we include all cases in which satisfactory progress is made on a regimen consisting of the usual therapeutic measures. This category would include most cases of minimal pulmonary tuberculosis. Although sometimes lesions in such cases heal exceedingly slowly, it is generally agreed that most minimal lesions in the lung will undergo spontaneous regression or become arrested under favorable conditions. In the few cases of minimal pulmonary lesions in which streptomycin has been used, it would be difficult to prove that streptomycin accelerated the healing process. Inasmuch as the toxicity of streptomycin is being treated as a separate subject in this symposium, it will not be discussed here except to say that the potential toxicity appears to be sufficient to deny the drug to patients who can make a satisfactory recovery without it. The danger is not sufficient to justify denying streptomycin to any patient who is likely to obtain appreciable gains from such treatment.

At present we do not consider chronic fibrocaseous pulmonary tuberculosis suitable for treatment with streptomycin unless there is a conspicuous component of more recent exudative disease. Also, our experience has indicated that it is useless to expect streptomycin to be effective in obviously terminal cases of destructive types of pulmonary tuberculosis.

Tuberculous empyema is another condition in which treatment with streptomycin has been disappointing, whether the drug is administered parenterally, intrapleurally or by both methods. Possibly this is due to the fact that purulent empyema fluid is usually frankly acid in reaction, whereas streptomycin is more effective in an alkaline solution. In our series of seven cases, treatment was truly successful in only one case. This patient had tuberculous empyema complicated by a bronchopleural fistula and several draining sinuses of the chest wall. She had been under our observation for four years, in the course of which she had undergone several surgical procedures without any improvement in her condition. She received 1.2 Gm. of streptomycin daily, and in addition a 1 per cent solution of the drug in physiologic saline solution was sprayed into the empyema cavity several times day. The bronchopleural fistula closed within three weeks, the chest wall healed soon afterward, and it was impossible to recover Mycobacterium tuberculosis from the pleural fluid after three months of treatment. At present, ten months after cessation of treatment with streptomycin, the infection has not recurred. When tuberculous empyema is refractory to other methods of treatment, a trial of streptomycin may be worth while. It will be interesting to note the experience of other investigators who may be able to improve on our methods of employing streptomycin in cases of tuberculous empyema.

It must always be emphasized that treatment with streptomycin is not a substitute for rest in bed and sanatorium care, which are still fundamental in the treatment of tuberculosis. Nor can it be expected to supersede collapse therapy and other surgical procedures when these are indicated.

## REASONS FOR LIMITATIONS OF TREATMENT WITH STREPTOMYCIN

The limitations of treatment with streptomycin are due to several factors probably inherent in any form of antibacterial therapy for tuberculosis. In the first place, the tissue changes in this disease tend to be destructive and proliferative. Older lesions, especially, are relatively avascular and, therefore, difficult of access for a blood-borne antibacterial substance.

In the second place, streptomycin is predominantly bacteriostatic rather than bactericidal. Youmans[12] found that of a total of fifty-eight human and bovine strains of tubercle bacilli, the growth of 70.8 per cent was inhibited by less than 1 microgram of streptomycin per milliliter of media. On the other hand, a concentration of more than 50 micrograms per milliliter was necessary to produce a bactericidal effect on the tubercle bacillus. The behavior of the drug *in vivo* seems to parallel its activity *in vitro*. The bacteriostatic action produces a limited suppressive effect on the disease and allows the patient to muster his natural defense forces. If these are sufficient and if the disease process is essentially curable, the ultimate result of treatment with streptomycin probably will be good.

In the third place, the therapeutic potentialities of streptomycin are limited because the duration of bacteriostatic action is limited. After prolonged exposure to streptomycin, strains of Mycobacterium tuberculosis may be isolated which are several thousand times as resistant to the effects of the drug as those isolated originally. This problem of drug fastness appears to be paramount at present. The relation of dosage to the factor of resistance has not been determined, but apparently a dose as large as 3 Gm. a day will not prevent its occurrence. Fortunately, the tubercle bacillus multiplies at a leisurely rate, so that resistance to an antibacterial agent does not become a problem so soon as in the case of other bacteria. From data available at present, the period from the beginning of treatment to the appearance of resistant strains varies from one to several months. Sometimes a resistant strain of Mycobacterium tuberculosis may be recovered from a patient and subsequently strains sensitive to streptomycin may be recovered following cessation of treatment. Patients may benefit from a second course of treatment with streptomycin for recurrent tuberculosis. Whether the problem of resistance to streptomycin can be circumvented remains to be seen. A second antibacterial agent is now being used in conjunction with streptomycin in hope of retarding or preventing development of resistant strains. Variations in dosage schedule are also being employed.

## SUMMARY

Streptomycin is the most effective antibacterial agent known for tuberculosis. *In vitro* it has a marked bacteriostatic action on the tubercle bacillus, and *in vivo* it tends to exert a deterrent effect on the disease in both animals and man. Its therapeutic value is limited by the fact that after exposure to streptomycin for weeks or months, strains of Mycobacterium tuberculosis which are resistant to the effects of the drug may be isolated. Hence streptomycin is of most value in conditions in which temporary suppression of the infection will enable the patient to gain the ascendency over his disease; healing then occurs by natural processes.

Prolonged arrest of the disease has been achieved by treatment with streptomycin even in cases of hematogenic tuberculosis, including generalized miliary tuberculosis and tuberculous meningitis. For these conditions large doses of streptomycin must be given parenterally for several months, and for meningitis intrathecal injections are imperative also during the early weeks of treatment. Other types of tuberculosis which have responded to treatment with streptomycin include exudative pulmonary disease, ulcerating lesions of the respiratory tract and tuberculous draining sinuses. It has some place in the treatment of bilateral renal tuberculosis or tuberculosis of a solitary kidney. It also is used before and after thoracic surgery for pulmonary tuberculosis. Because of the potential toxicity,

use of the drug probably is contraindicated in conditions which will respond satisfactorily to the usual methods of treatment.

Our knowledge of streptomycin is still in a state of flux. Now that the drug is undergoing extensive clinical investigation in many institutions its ultimate place in the treatment of tuberculosis will be determined in time. Experience with this antibiotic agent has proved that tuberculosis is a disease amenable to antibacterial therapy and it is hoped that other usable agents will be forthcoming.

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# Use of Streptomycin in the Treatment of Bacterial Endocarditis*

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FEW reports[1,2] have appeared concerning the treatment of bacterial endocarditis with streptomycin. Since the great majority of cases are caused by streptococci which are sensitive to penicillin and can be cured by this drug, only occasional cases require other forms of therapy.

The first and most obvious cases in which streptomycin seems to be the drug of choice are those in which the causative agent is a streptomycin-sensitive gram-negative bacillus. These organisms are almost without exception unaffected by penicillin, and many of them exhibit high resistance to sulfonamides. Furthermore, the latter drugs have been shown[3] to diffuse poorly into fibrin and probably do not reach the depths of vegetations readily.

The second category of bacterial endocarditis in which streptomycin therapy must be considered consists of the small fraction, perhaps 10 per cent, of cases of non-hemolytic streptococcus endocarditis in which the organism is resistant to penicillin from the start plus the still smaller fraction whose organism becomes resistant during penicillin therapy.

Six cases falling in one or another of these categories have been treated with streptomycin at the Presbyterian Hospital. One of these has already been reported.[2] This patient, with classical bacterial endocarditis due to an unidentified gram-negative bacillus, was treated with streptomycin, 3 Gm. a day for ten days following an eighteen-day course of sulfadiazine. He has now been followed for seventeen months without clinical or bacteriological evidence of relapse. Brief summaries of the remaining five cases are presented.

## CASE REPORTS

CASE II. J. B., a fifty-seven year old male, with no history of previous heart disease, was admitted to the urological service of the Presbyterian Hospital in January, 1946, because of an infected diverticulum of the urinary bladder which was excised on February 8, 1946. Following the operation he developed a swinging fever and B. pyocyaneus was repeatedly grown both from the wound and from the blood cultures. The course was uninfluenced by sulfadiazine and under observation he developed a harsh apical systolic murmur. The organism required 15 micrograms of streptomycin for inhibition *in vitro* throughout. Streptomycin, 3 Gm. a day, 0.5 Gm. every four hours intramuscularly, was started on February 21st and continued for fourteen days following which the dosage was increased to 4 Gm. a day for five more days. The patient improved clinically and, after the first week of therapy blood cultures were sterile, but he continued to have lowgrade fever. The day after streptomycin was stopped the temperature again rose to 103° F. and blood culture was positive. On March 15th, therapy was resumed, this time with 6 Gm. of streptomycin a day, and was continued for seven days, but fur-

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The streptomycin was provided in part by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

ther treatment was not considered advisable since blood cultures continued positive in the face of such large doses of the drug. The patient died on April 22nd and at autopsy was found to have a large friable vegetation on an otherwise normal mitral valve.

Case III. T. P., a fifty-one year old Italian barber, was admitted to the Presbyterian Hospital in August, 1946, with a six months' story of weight loss, night sweats and easy fatiguability. Though there was no history of rheumatic fever, he had the murmurs of mitral valvular disease. In addition, there were low-grade fever, clubbing of the fingers, and a palpable spleen. At first the diagnosis was in doubt and a complete workup for fever of unknown origin was essentially negative until finally a gram-negative bacillus grew out in several blood cultures. The organism has not been positively identified, but is not one of the commonly encountered groups. It grew so slowly that *in vitro* tests of sensitivity were of doubtful value, but it was inhibited by 1 or 2 micrograms of streptomycin, whereas cultures had been positive while the patient was receiving 1,600,000 units of penicillin daily and the organism appeared to be resistant to this drug. Accordingly, he was started on streptomycin, 3 Gm. daily, 0.5 Gm. every four hours intramuscularly, and this was continued for three weeks during which time his temperature fell to normal, the blood cultures became sterile and have remained so to the present, two months after cessation of therapy. On the eighteenth day of therapy dizziness and unsteadiness of gait appeared. Vestibular tests showed a complete loss of response at this time, but audiograms showed no change. Since he showed some evidence of spinocerebellar involvement as well, a lumbar puncture was done, revealing normal findings except for a spinal fluid protein of 80 mg. per cent. The patient's subsequent course has been marked by slow subjective improvement in the unsteadiness, with loss of all vertigo. Spinal fluid examination was repeated two weeks later and again showed a protein of 75 mg. per cent. The explanation for this spinal fluid abnormality is not clear, but it occurred at a time when the patient had no signs of uncontrolled infection and was not having evident embolic phenomena. Whether or not it is connected with toxicity of streptomycin remains obscure.

Case IV. H. E., a forty-nine year old negro male, was admitted to the Presbyterian Hospital in March, 1945. Although he had no history of rheumatic fever there was a harsh apical systolic murmur and he had had fever and malaise for four months. Blood cultures had repeatedly grown a hemolytic streptococcus at another hospital where he had received penicillin, 200,000 units a day, plus sulfapyridine without even temporary sterilization of the blood stream. The organism recovered at this hospital proved to be a hemolytic streptococcus of the Lancefield group D which required 3 units per cc. of penicillin or 8 micrograms per cc. of streptomycin for inhibition of growth *in vitro*. During the next three months he received three courses of penicillin by constant intramuscular and intravenous drip consisting of 5,000,000 units a day for twelve days, then 10,000,000 units a day for fourteen days on two occasions. In each instance the blood cultures were sterile during therapy but became positive within four or five days of stopping. Finally, in August, 1945, he was given streptomycin, 3 Gm. a day, by constant intravenous and intramuscular drip for fourteen days. Daily blood levels of streptomycin averaged 51 micrograms per cc. varying between extremes of 22 and 96. Blood cultures remained sterile during therapy and for four days after but on the seventh day were again positive. No further treatment was attempted because the patient's general condition had deteriorated badly by this time. He was transferred to another hospital where he died six weeks later. No autopsy was performed.

Case V. I. H., a twenty-six year old nurse, with known mitral disease, was admitted to the Presbyterian Hospital in February, 1946, with an eight months' story of chills, fever, embolic phenomena and weight loss. The diagnosis of bacterial endocarditis had been established by repeated positive blood cultures at another hospital where she had been given intensive penicillin treatment over a period of two months with daily doses up to 2,200,000 units a day. In spite of this, blood cultures had been positive throughout. The organism proved to be a

Streptococcus fecalis of Lancefield group D which required 8 units of penicillin and 3.5 micrograms of streptomycin *in vitro* for inhibition. Since the organism appeared to be more susceptible *in vitro* to a combination of the two antibiotics than to either alone, it was decided to give the patient 4 Gm. of streptomycin plus 4,000,000 units of penicillin a day for four weeks. At first the drugs were combined in a single infusion of saline but on the sixth day, the patient's temperature spiked to 105° F. and it was noted that there was a precipitate in the flask. Subsequently, penicillin was given by constant drip, either intravenous or intramuscular, and streptomycin was injected intramuscularly every three hours. In the third week, she complained of transitory dizziness on two occasions when out of bed but otherwise her course was one of steady improvement. Blood cultures have all been sterile since therapy began. She has now been followed for ten months post-therapy and is leading a normal life free from evidence of infection. She has complained of slight unsteadiness of gait especially in the dark which has slowly improved. Unfortunately, it has not been possible to get tests of vestibular function, but it seems likely that these symptoms represent the toxic effect of streptomycin.

Case VI. E. H., a sixty-eight year old male, was admitted to the Presbyterian Hospital in October, 1946, with a diagnosis of bacterial endocarditis of three months' duration. There was no history of rheumatic fever but he showed the signs of mitral disease without evidence of cardiac failure. Blood cultures had been repeatedly positive at another hospital and a Streptococcus viridans persisted in the blood stream during therapy with 100,000 units of penicillin every three hours. The organism proved to be an enterococcus of Lancefield group D requiring 1.0 unit of penicillin or 20 micrograms of streptomycin for inhibition of growth *in vitro*. He was first given 700,000 units of penicillin every three hours intramuscularly (5,600,000 units daily) for three weeks during which time blood cultures were sterile and the patient clinically improved. Cultures became positive again one week later, the organism now requiring 1.0 unit of penicillin or 30 micrograms of streptomycin for inhibition. He was next given 20,000,000 units of penicillin daily for sixteen days and again there was clinical improvement. Blood cultures were sterile during therapy and penicillin serum levels reached as high as 100 units per cc. Two weeks after this course the patient continued afebrile and felt well, but blood cultures again were positive, the organism now requiring 10 units of penicillin or 40 micrograms of streptomycin for *in vitro* inhibition. Although it seemed unlikely that streptomycin would be effective, it was then administered in doses of 6 gm. daily, but since blood cultures continued positive in the face of therapy, it was abandoned after one week. The course subsequently was slowly downhill in spite of a trial on bacitracin and blood cultures were persistently positive. Organisms recovered from the blood after streptomycin administration required more than 100 micrograms of the drug for inhibition of growth *in vitro*. At autopsy a large vegetation was present on the mitral valve; microscopic findings have not yet been reported.

In summary, of our three cases due to gram-negative organisms, treatment with streptomycin appears to have effected cure in two patients and failed in one instance. Of the three patients infected with penicillin-resistant streptococci, only one responded to streptomycin and this patient received large doses of penicillin in conjunction.

Dr. Chester S. Keefer has kindly supplied us with reports on twelve additional cases treated at various clinics throughout the country under the program for clinical trial of streptomycin (Cases 7–18, Table 1). Five patients had endocarditis due to various types of gram-negative bacilli. Of these three were definite failures, one patient with H. influenzae endocarditis was probably cured on streptomycin in combination with sulfadiazine, and one patient with infection due to an unidentified microaerophilic gram-negative bacillus appears to be well after a course of penicillin followed by streptomycin. The exact rôle of strepto-

mycin in the last two cases cannot be definitely determined, but it probably contributed to the favorable results.

In the remaining seven patients, the causative organisms were gram-positive cocci. One patient, with a staphylococcal endocarditis due to an organism which was penicillin-resistant but sensitive to 0.4 microgram of streptomycin, was apparently cured after a course of 1.5 to 3 Gm. daily for twenty-eight days. Of four patients harboring a penicillin-resistant Streptococcus viridans, two appear to be cured. One patient's organism was sensitive to 5 micrograms of streptomycin *in vitro*, and he received 3 Gm. daily for thirty-four days. The second patient received 3.0 Gm. the first day followed by 1.0 Gm. daily for fifteen days; the *in vitro* sensitivity in this patient is not recorded.

The two remaining patients had infections caused by enterococci. In one temporary sterilization of the blood stream was obtained, but the patient had a recurrence of infection three months later. On subsequent treatment, the infection persisted and culminated in death in spite of the administration of doses up to 8 Gm. of streptomycin per day. In this case during the second course of streptomycin, the organism at the beginning was reported as sensitive to 0.2 micrograms of the drug, but later is said to have required seventy-five times as much by *in vitro* test. The second case of enterococcus infection failed to respond to therapy though 3 Gm. daily were administered in two courses of two weeks each. Data on sensitivity of the organisms are not available.

Combining the figures on all cases reported, of eighteen cases treated probable cure has been the result in eight. The rôle of streptomycin is open to some question in four of these eight. The remaining ten cases were definite failures at the dosages employed.

It will be noted in Table 1 that seven patients showed the common toxic manifestations of streptomycin due to vestibular damage, and that there is a rough correlation with total dosage and duration of therapy. It is probable that other cases would have shown damage to the eighth nerve had routine function tests been employed. In only two patients was there definite evidence of decreased auditory acuity. In one of these (Case 12) it may be significant that there was renal damage with nitrogen retention at the beginning of therapy. The other (Case 7) may not be attributable to streptomycin, as symptoms of tinnitus and deafness are reported to have been present from the onset of streptomycin therapy, which is an unusual time relation for this toxic manifestation. Other toxic effects noted occasionally in the series were rashes, fever, pain at sites of injection, headache and flushing, none of which were alarming although the patient receiving 8 Gm. a day experienced extreme prostration and tachycardia of such severity that treatment was discontinued. No patients in this group showed renal damage which could be attributed to streptomycin.

## COMMENT

At present, it is impossible to make definite statements as to the precise place of streptomycin in the treatment of bacterial endocarditis. Certainly penicillin is the drug of choice for the majority of cases. In the rare case in which the infecting organism is resistant to penicillin or in those instances in which maximal doses of penicillin have failed, streptomycin offers some hope. The value of *in vitro* tests of streptomycin-sensitivity in predicting the outcome of therapy cannot yet be determined but it is to be noted that, in the present series, treatment was not successful in any case in which the organism required more than 8 micrograms per cc. for *in vitro* inhibition of growth.

TABLE I

PATIENTS WITH BACTERIAL ENDOCARDITIS TREATED WITH STREPTOMYCIN

| Case No. | Infecting Organism | | Streptomycin Therapy | | | Result | Toxicity | Remarks |
|---|---|---|---|---|---|---|---|---|
| | Type | Streptomycin Sensitivity $\mu$/cc. | Daily Dose Streptomycin (Gm.) | Duration of Therapy (Days) | Total Dose (Gm.) | | | |
| 1. | Unidentified gram-negative bacillus | 3.75 | 3 | 10 | 30 | Cure | Histamine-like | Also received sulfadiazine |
| 2. | B. pyocyaneus | 15 | 3–6 | 27 | 104 | Failure | Severe vestibular | |
| 3. | Unidentified gram-negative bacillus | 1–2 | 3 | 21 | 63 | Cure? | Vestibular | 2 months follow-up |
| 4. | Enterococcus | 8–40 | 3 | 14 | 42 | Failure | ..... | Blood level averaged 51 |
| 5. | Enterococcus | 3.5 | 4 | 32 | 125 | Cure | Vestibular | Penicillin also given |
| 6. | Enterococcus | 20–<100 | 6 | 7 | 42 | Failure | ..... | Organism became fast |
| 7. | Unidentified gram-negative bacillus | 1–16 | 2.5 | 40 | 100 | Failure | Vestibular and auditory, marked | Temporary response, organism became resistant |
| 8. | H. influenzae | 1.5–2 | 2 | 10 | 20 | Cure | ..... | Also penicillin and sulfadiazine |
| 9. | B. aerogenes | ..... | 2 | 7 | 14 | Failure | | |
| 10. | Ps. aeruginosa | 40 | 2–4 | 24 | 88 | Failure | | |
| 11. | Unidentified gram-negative bacillus | 7 | 2.6–3.2 | 20 | 50 | Cure? | Vestibular | Penicillin also |
| 12. | Staph. aureus | 0.4 | 1.5–3 | 28 | 72 | Cure | Vestibular and auditory, improving | Penicillin sensitivity 10 units |
| 13. | Strep. viridans | 5 | 2 | 14 | 28 | Failure | | |
| 14. | Strep. viridans | 5 | 3 | 34 | 102 | Cure? | Vestibular | 3 months follow-up |
| 15. | Strep. viridans | ..... | 3 for 1 day, then 1 | 15 | 17 | Cure? | ..... | 3 months follow-up |
| 16. | Strep. viridans | ..... | 2 | 17 | 33 | Failure | | |
| 17. | Enterococcus | a) 4 | 4 | 5 | 20 | Remission 3 months | ..... | Blood levels 25–50 |
| | | b) 0.2–15 | 1–8 | 28 | 72.5 | Failure | Fever and prostration on 8 Gm. | Blood levels up to 180 |
| 18. | Enterococcus | ..... | 3 | 32 | 105 | Failure | ..... | Temporary clinical improvement |

Decisions as to dosage and duration of therapy must still be made largely on the basis of analogy with the use of penicillin in this disease. Treatment should probably be continued for three to four weeks at a daily dosage of from 2 to 6 Gm. Although this means that one can expect almost uniform appearance of vestibular damage and probably a significant incidence of nerve deafness, there are obvious reasons for accepting these risks. In the first place, patients with an established diagnosis of

bacterial endocarditis which is not amenable to therapy with penicillin have a virtually hopeless prognosis without streptomycin. Secondly, large doses of streptomycin are recommended because of the marked tendency of bacteria to become resistant to this agent when exposed to it in sublethal concentrations. The suggested duration of therapy is based mainly on experience with penicillin treated cases, and is therefore quite tentative. Though one would feel safer in continuing a course of streptomycin for three or four weeks, in individuals who appear to be doing well but who develop evidence of eighth nerve deafness after two weeks, it may be wise to stop at that point, for the acoustic damage has been shown to regress if the drug is promptly withdrawn.

What will be accomplished in difficult cases with combinations of two or more antibiotics administered together remains to be seen, but there are reasons for believing that such an approach might be fruitful. In cases treated with a single drug some therapeutic failures seem to be caused by the persistence of a very small number of the original population of organisms. These may be a few bacterial cells which in the beginning were more resistant to the antibiotic than their fellows, or they may be cells in a temporary phase of resistance. In either event it seems reasonable to suppose that if they were caught in a crossfire of two antibiotics acting at the same time but in different manners, the chances of their survival might be lessened. Furthermore, certain individual cells in a bacterial population might be able to resist the action of penicillin but would succumb to streptomycin, while at the same time other individuals might do the reverse. It is important to note that such events could be taking place and not be apparent in the *in vitro* determinations of sensitivity. As usually performed, these tests tell one only what happens to the great majority of the cells in a culture, and a few slow-growing individuals could be missed. In this connection, it is of interest to note that in some patients with bacterial endocarditis in early relapse after the penicillin therapy, blood cultures had to be incubated for almost three weeks before growth was detectable.

## RECOMMENDATIONS

Tentative recommendations as to the use of streptomycin in bacterial endocarditis may be stated as follows:

1. The infecting organism should, whenever possible, be isolated and its sensitivity to streptomycin and penicillin determined.
2. In most cases of non-hemolytic streptococcus endocarditis, penicillin in large dosage is the drug of choice.
3. The following varieties of bacterial endocarditis should be given a trial with streptomycin therapy: (1) Infections due to gram-negative bacilli; (2) infections due to penicillin-resistant gram-positive cocci, and (3) infections which have failed to respond to maximal penicillin therapy.
4. Dosages of from 2 to 6 Gm. daily for two to four weeks should be used, depending on the sensitivity of the organism and the clinical response.
5. It is important that large doses be given from the start of treatment because of the marked tendency of organisms to develop resistance to streptomycin.
6. A high proportion of patients so treated must be expected to show vestibular damage, and a few may show nerve deafness as a result of streptomycin toxicity. Audiometric and vestibular function tests should be done before therapy and at weekly intervals during treatment with streptomycin.
7. In clinically resistant cases of endocarditis caused by organisms which show some *in vitro* sensitivity to both penicillin

and streptomycin, a course of therapy with both drugs together should be tried.


## SUMMARY

Results of treatment of eighteen cases of bacterial endocarditis with streptomycin are presented and discussed. Eight patients appear at present to be cured. Indications for the use of streptomycin in bacterial endocarditis are considered and tentative recommendations for treatment made.


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# Streptomycin in Peritonitis*

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PERITONEAL infections have always been difficult to treat clinically. There can be no doubt but that the sulfonamides and penicillin have been useful in the treatment of peritonitis, but it cannot be said that these agents control all peritoneal infections even when they are used in addition to adequate surgery and adequate supportive therapy. Because of their limited antibacterial activity neither penicillin nor the sulfonamides would be expected to control completely peritoneal infections of mixed gram-positive and gram-negative organisms. Also it is well recognized that some of the body exudates have an inhibitory effect on the sulfonamides and that the action of penicillin is inhibited by certain bacterial products.

Streptomycin, because of its range of antibacterial activity, would appear to be an ideal agent with which to treat mixed peritoneal infections. Streptomycin is not destroyed by body exudates nor by the action of bacteria or bacterial products. Preliminary clinical experience and a more extensive experience in the treatment of experimental peritonitis indicate that streptomycin is useful in the treatment of peritonitis.

Keefer[1] reported on the treatment of fifty-three patients with peritonitis in his report of the first 1,000 patients treated with streptomycin under the direction of the Committee of Chemotherapeutics and Other Agents of the National Research Council. He points out the difficulty of evaluating the precise rôle of any form of chemotherapy in the treatment of peritonitis for the reason that there are so many variables concerned in recovery from this type of infection. Of the fifty-three patients with peritonitis thirty-nine recovered. Of the twenty-one patients with peritonitis following appendicitis three died. Of nine patients with peritonitis which we have treated with streptomycin or a combination of streptomycin and penicillin only one patient has died. This patient had a carcinoma of the sigmoid colon which ruptured several days before admission to the hospital. Following surgical drainage of the abdomen the patient lived for forty-six days and finally succumbed to multiple abdominal abscesses. One of the abscesses communicated with the colon presumably at the point of the original perforation. Because of the difficulty of evaluation of the many variables in the treatment of peritonitis clinically, an attempt was made to determine the relative usefulness of streptomycin and streptomycin in combination with various other antibacterial agents in the treatment of experimental peritonitis in animals.

Murphy, Ravdin and Zintel[2] demonstrated that streptomycin is effective in the treatment of experimental peritonitis in dogs. Streptomycin therapy in the dosages used resulted in a 40 per cent greater survival rate in the treated group than in the control group. Penicillin therapy according to the data of Fauley et al.[3] produced a 34.2 per cent greater survival rate in the treated animals than in the control animals if the animals which developed fistulas were not excluded. Although the Fauley technic was used by both groups of investigators, their

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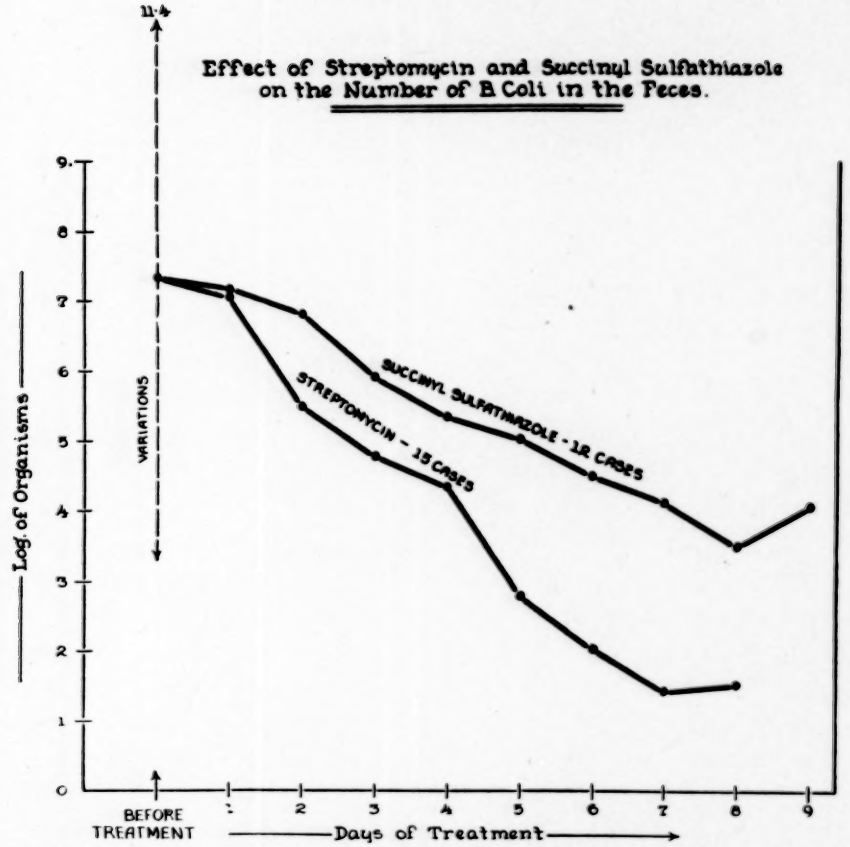


FIG. 1. Effect of streptomycin and succinylsulfathiazole on the number of B. coli in the feces.

results cannot be compared directly because of the discrepancy in the survival rates of the respective control groups, namely, 7.4 per cent reported by Fauley et al. and 30 per cent reported by Murphy et al. Bower et al.[4] found that 50 per cent of the animals treated with sulfanilamide lived whereas 91.7 per cent of his control animals with experimental peritonitis died. Thus in the hands of different investigators sulfonamides, penicillin and streptomycin have each produced survival rates 34 to 41.7 per cent greater than the respective control survival rates.

Further experiments were designed to compare the effectiveness of combinations of the chemotherapeutic and antibiotic agents. Although the use of multiple agents in the treatment of infections has not been recommended in the past, there are some indications that may justify multiple therapy. The use of several agents with different ranges of antibacterial activity might well be considered reasonable in the treatment of peritonitis which is usually an infection of several types of gram-positive and gram-negative organisms. The use of such combinations of agents might further be justified by the fact that often it is not possible to know the complete bacteriological picture of peritoneal infections and, therefore, is impossible to know whether a therapeutic response could be expected from a single chemotherapeutic or a single antibiotic agent. Furthermore, it has been shown by Nichols[5] that penicillin and streptomycin have a synergistic action against certain bacterial organisms and certain combinations of bacterial organisms. In other words, the actions of penicillin and streptomycin under given conditions are more than

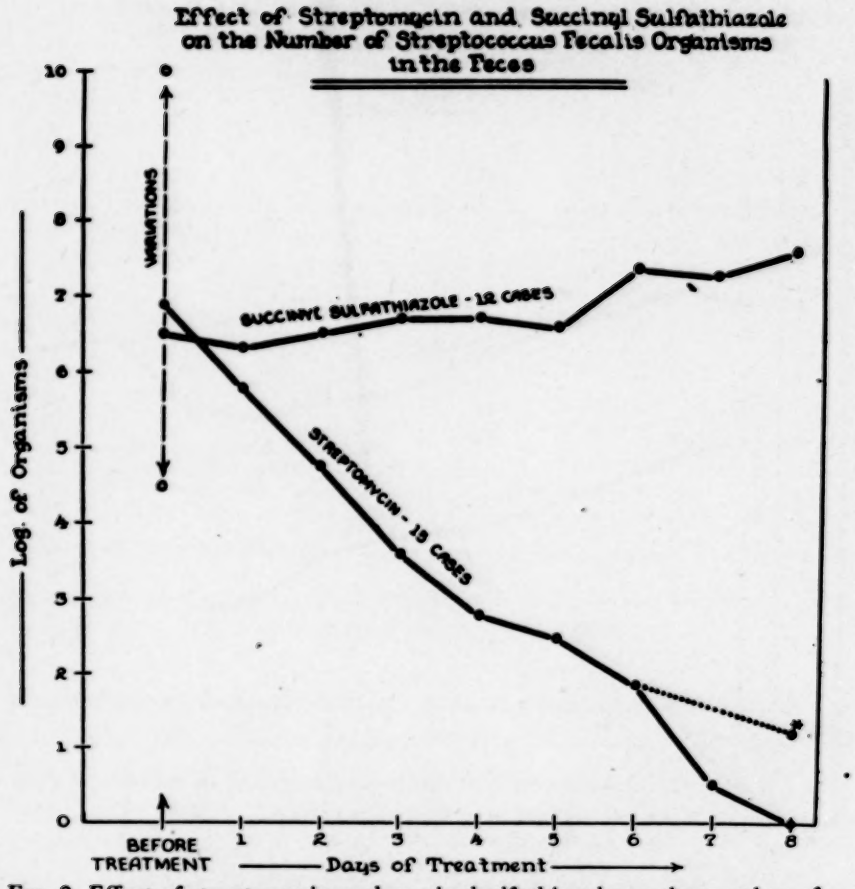


FIG. 2. Effect of streptomycin and succinylsulfathiazole on the number of Streptococcus fecalis organisms in the feces.

additive. Finally Carpenter[6] has shown that the ability of a given organism to develop resistance *in vitro* is almost abolished by subjecting the organism to several antibacterial agents simultaneously.

Five groups of animals were used to compare the effectiveness of streptomycin with various combinations of antibacterial agents in the treatment of peritonitis. A more virulent type of peritonitis was produced in these animals than is produced by either the Bower or the Fauley technic and, therefore, the following figures cannot be compared with those cited in the preceding discussion. In our experiments, after ligating the blood supply to the appendix with silk ligatures, the base of the appendix was ligated with umbilical tape. The appendix was opened along its entire length. With the aid of an Allis clamp the peritoneal cavity was contaminated with the appendiceal contents. Finally, after closing the abdominal wound, the dogs were given 55.0 cc. of castor oil. The survival rate following streptomycin therapy was 27.4 per cent as compared to the control survival rate of 6.6 per cent. Streptomycin alone was not as effective as was the combination of local sulfanilamide, systemic sodium sulfadiazine and systemic penicillin, as evidenced by a survival rate of 40 per cent following the combined therapy.[7] Sixty per cent of the animals survived when streptomycin therapy was added to the local sulfanilamide, systemic sodium sulfadiazine and systemic penicillin therapy. Thus streptomycin had an added protective effect over and above that afforded by the sulfonamides and penicillin in the dosages used. Finally,

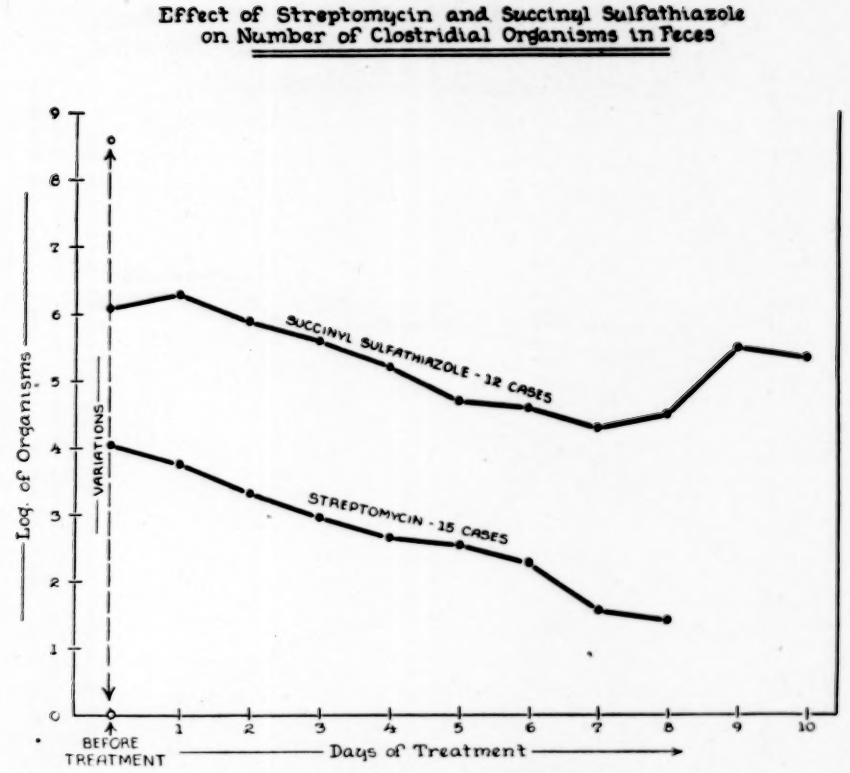


FIG. 3. Effect of streptomycin and succinylsulfathiazole on number of clostridial organisms in the feces.

the survival rate of 70 per cent in the animals treated only with penicillin and streptomycin systemically[8] was greater, but not significantly greater, than the 60 per cent survival rate observed in the animals treated with local sulfanilamide, systemic sodium sulfadiazine, systemic penicillin and systemic streptomycin. On the basis of these experiments the combination of penicillin and streptomycin would appear to be as effective as any of the other combinations of antibacterial agents used.

## PROPHYLACTIC STREPTOMYCIN PRIOR TO LARGE BOWEL SURGERY

Streptomycin when administered by the oral route appears to be the most effective agent for reducing the relative number of bacterial organisms in the feces. Following oral administration 95 to 98 per cent of the streptomycin is recovered in the feces. Concentrations of from 4,000 to 13,000 micrograms of streptomycin per Gm. of feces are usually attained after the administration of 1.0 Gm. of antibiotic daily for several days. Since streptomycin is not destroyed appreciably by the gastric juices, it can be administered, dissolved or suspended, in any liquid such as milk, fruit juice, etc. There seems to be no difference in antibacterial effect whether it is given in four divided doses every six hours or whether it is administered in three divided doses—one with each meal. Oral streptomycin is more potent than succinylsulfathiazole in its effect on the bacterial flora of the stools. Streptomycin is not only more effective in reducing the number of Bacillus coli organisms, but it is also more effective in reducing the number of Streptococci fecalis and Clostridial organisms than is succinylsulfathiazole. Although some organisms completely disappear from the stools, complete sterilization of the large bowel was not attained. Using

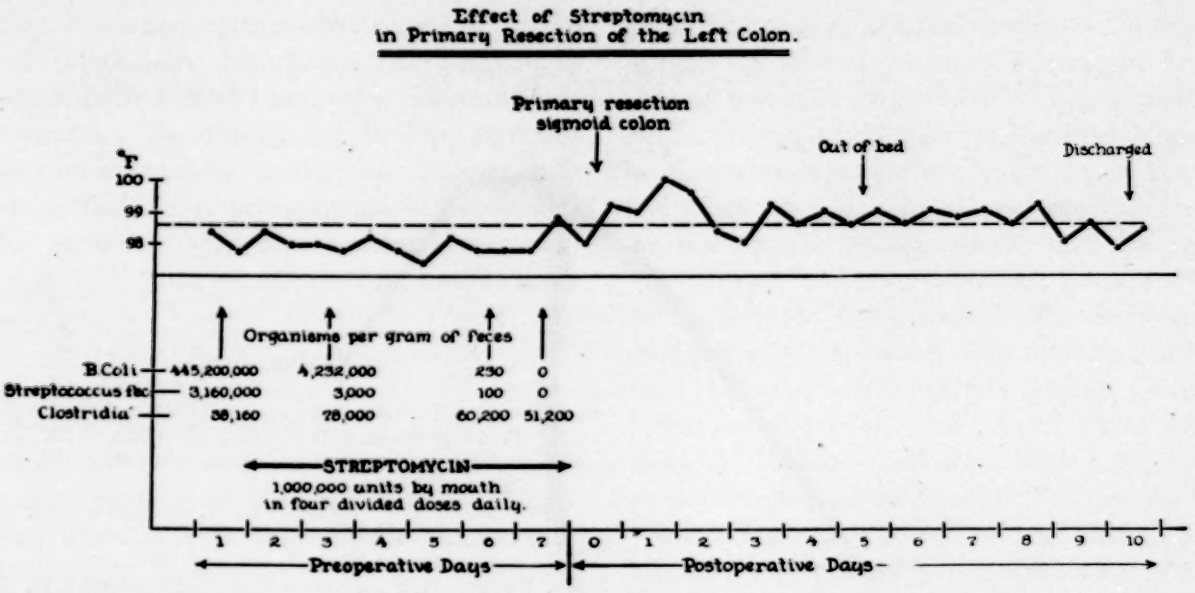


FIG. 4. Preoperative and postoperative effect of streptomycin in a patient who had a primary resection and anastomosis of the sigmoid colon.

massive doses of streptomycin, succinylsulfathiazole and sulfaguanidine, Smith and Robinson[9] were unable to sterilize the feces of rats. There is reasonable doubt that complete sterilization can be attained since occasional strains of bacterial organisms found in the feces are resistant to the action of streptomycin and to sulfasuxidine.

Streptomycin was administered in doses of 1.0 Gm. per day to fifteen patients for periods of from six to ten days. Quantitative stool cultures were carried out by Miss Marjorie Wiley before treatment was started and at two-day intervals thereafter. By plating out stool suspensions on differential media, counts were obtained for the coliform group of organisms, Streptococcus fecalis and Clostridia. The results were compared with similar data obtained by Lockwood and Zintel[10] previously with succinylsulfathiazole. With both drugs, occasional patients show marked deviations from the mean. The logarithms of the counts were plotted against time of drug administration and an average curve was drawn for each drug and each group of organisms. The relative effectiveness of succinylsulfathiazole and streptomycin on Bacillus coli, Streptococcus fecalis, and the clostridial organisms is shown in Figures 1, 2 and 3. The figures used are the average of the logarithms, not the logarithm of the averages. Streptomycin, even in the limited dosage employed, was much more effective than was succinylsulfathiazole.

The argument in favor of the prophylactic use of agents to reduce the number of bacterial organisms in the large bowel contents prior to elective surgery is largely a theoretical one but with apparent practical importance. The mortality rate of peritonitis following elective surgery of the large bowel at the Hospital of the University of Pennsylvania in the last three years prior to the use of streptomycin was but 1 per cent. Several thousand cases would be required to demonstrate a significant difference in mortality rate between patients who received oral streptomycin and those who did not.

It is well known that in animal experiments the possibility of producing an infection depends upon three variables: (1) the virulence of the organisms, (2) the resistance of the host, and (3) the number of bacteria

present. Granted faultless surgical technic and supportive therapy, including chemotherapy and antibiotics, the first two factors would be fixed for any given patient. The last factor, that of the number of organisms present, may be altered by the preoperative use of oral streptomycin. Regardless of whether an open or a so-called "aseptic," or closed, method is used, some bacteria of the bowel content gain access to the peritoneal cavity during any operative procedure on the large bowel. In the very occasional patient, regardless of the operative method, there is gross spillage of fecal material. A very small percentage of patients may have fecal contamination secondary to necrosis of the tissue or leakage of the suture lines after operation. It seems reasonable to assume that the patient who has had the bacterial content of his fecal stream reduced approximately 180,000 times (as in the case of Bacillus coli) will have a better chance of escaping peritonitis than the patient who did not have the benefit of preoperative oral streptomycin.

We believe that with the aid of the antibiotic agents we are able to do a greater number of large bowel resections with primary suture. Figure 4 shows the preoperative and postoperative course of a patient who had a resection and primary suture of the bowel for carcinoma of the sigmoid colon, who was prepared with streptomycin orally and who received streptomycin and penicillin postoperatively. Although the total number of patients treated with streptomycin orally is much too small to attempt to draw any conclusions, we have been impressed with the smoothness of their postoperative courses and the absence of evidences of peritoneal infection.

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# Topical Use of Streptomycin in Wounds*

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AFTER the demonstration by Florey and Cairns[1] that the topical application of penicillin would not hasten the resolution of established infection in wounds, the reason for this failure was sought. Penicillinase,[2] a powerful substance that destroyed penicillin, was known to be elaborated by and was finally isolated from the gram-negative bacilli.[3] The gram-negative bacilli E. coli, pyocyaneus, proteus, etc., which invariably come to inhabit the pus of infected wounds as contaminants of fecal origin and with enormous capacity to spread, are not destroyed by penicillin. Their persistence, therefore, seemed to explain why the gram-positive bacteria continued to proliferate in spite of the addition of penicillin to the wound.

This failure of penicillin to cure by topical application the established localized infection in the wound must not be confused with its excellent efficacy to combat wound cellulitis and septicemia when administered parenterally.

With this background, the best approach to rid the wound of penicillinase seemed to be to destroy the gram-negative bacilli by using another antibacterial substance in conjunction with penicillin. Until this conclusion was reached, however, the need for an antibacterial to destroy only gram-negative bacilli had not received much attention although urologists had recognized the significance of this group of bacteria and had found them difficult to destroy in infections of the urological tract. In the "antiseptic era" antibacterial substances theoretically destroyed the gram-negative bacilli as well as others (and also the tissues) and later the failure of the sulfonamides, except for sulfamylon, to act in the presence of pus was attributed to para-aminobenzoic acid and not to any substance elaborated by the gram-negative bacilli.[4] True, the sulfonamides did not destroy the gram-negative bacilli in mixed infections but an adjunct antibacterial substance was not sought because of the apparent uselessness of the sulfonamides in the presence of pus.

Moreover, whether the gram-negative bacteria are really virulent or are simply contaminants of pus had often been discussed. They appear late in the pus and in spite of the fact that they finally dominate the flora. The granulations may grow abundantly and contraction takes place without interference.[5] Perineal wounds were pointed to as evidence that these micro-organisms did not interfere with healing. Gram-negative bacilli were always present in these wounds and yet they healed with bright red granulations. Some even believed that an enzyme secreted by the gram-negative bacilli, or in the inflammatory reaction to them, liquefied slough and that as soon as slough was liquefied the discharge of pus ceased. However, only one or two of the least common variety actually secrete a collagenase[6] so that the non-specific inflammatory reaction must be responsible for this enzymatic action.

The opponents to the thesis of the benignity of gram-negative bacilli pointed out that the profuse discharge produced in response to them depleted the serum protein of the patient, prevented the spread of skin

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grafts, and even liquefied grafts successfully transplanted.[7] They emphasized also that gram-negative infections do not clear up in tissues like bone which do not liquefy. Lastly, it cannot be denied that the exudative phase of healing of the perineal wound would be shorter if a non-toxic gram-negative antibacterial substance were used to prevent the initial multiplication of these bacteria.

In summary then, gram-negative bacilli do create infections in wounds and in the urinary tract, although this fact did not receive adequate attention until after an antibacterial substance was available to destroy gram-positive bacteria without interfering with the healing of the wound.

Before the isolation of streptomycin by Waksman,[8] no satisfactory antibacterial substance was found to destroy the gram-negative bacilli. Agents like acetic acid that were thought to be specific only decolored them. Most of the antibacterial substances tested for this purpose were either too toxic to cells and prevented wound healing or they destroyed penicillin. Penicillin is, of course, extremely sensitive to changes in environment. Suitable agents exhibiting low cell toxicity were difficult to find because the metabolism of the gram-negative bacilli more closely resembles the metabolism of the tissue cells than does that of the gram-positive bacteria.[9] All the common antiseptics except parachlorophenol failed on both scores and this substance was found to be mildly toxic to fresh tissues but not to granulations. Streptothrycin, first isolated by Waksman,[10] was somewhat compatible with penicillin but it was definitely toxic to cells and interfered with wound healing.[11]

Streptomycin, on the other hand, was not toxic to fresh cells in concentrations of 200 units per cc. and did not interfere with healing of the rabbit's ear wound.[11] Granulations are not affected by 1,000 units of streptomycin per cc. At a concentration of 200 units per cc., streptomycin was bactericidal after a short period of contact with the bacteria, acted in the presence of pus and to date there is no evidence that topical application produces untoward side effects. No cases of flushing, skin rashes or tinnitus have been encountered following local use of streptomycin. Neither Brown and Hinshaw[12] nor Fowler and Ewing[13] have reported otic complications from the local application of streptomycin. In all fairness, however, it must be noted that streptomycin has not been used in such large quantities topically, and that most patients have received the drug parenterally.

TABLE 1
STREPTOMYCIN 200 UNITS PER CC. 10 MINUTE CONTACT

| Strain of Bacteria | Inhibition of growth of bacteria in area contacted by paper | | Inhibition zone about this area |
|---|---|---|---|
| B. coli | ++++ | | ++ |
| B. coli | ++++ | | ++ |
| B. coli | ++++ | | + |
| B. proteus | ++++ | | + |
| B. proteus | ++++ | | + |
| B. proteus | ++++ | | ++++ |
| Staph. (coagulase positive) | ++++ | | ++ |
| Staph. (coagulase positive) | ++++ | | ++++ |
| Pyocyaneus | +++ | Spread in from edges | 0 |
| Pyocyaneus | +++ | Spread in from edges | 0 |
| Pyocyaneus | ++ | Overgrown in 36 hours | 0 |
| Streptococcus hemolytic | 0 | | 0 |
| Green streptococcus | 0 | | 0 |

The bacterial spectrum of streptomycin includes micro-organisms other than the gram-negative bacilli. In fact, it is more inclusive than penicillin but unfortunately streptomycin does not have a complete bacterial spectrum. In our own testing, both the hemolytic and green streptococci were not destroyed by the concentrations used. (Table 1). Pulaski[14] found that 80 per cent of

TABLE II

STREPTOMYCIN SENSITIVITY OF AEROBIC BACTERIAL FLORA OF 143 SURGICAL INFECTIONS

| Streptomycin units/cc. (*in vitro*) | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | 64 | 128+ | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| Gram-negative organisms | | | | | | | | | | |
| A. aerogenes | | 3 | 8 | 10 | 4 | 4 | 2 | 3 | 3 | 37 |
| Esch. coli | | 1 | 5 | 10 | 12 | 5 | 2 | | | 35 |
| Paracolon group | | | 5 | 3 | 7 | 3 | | 1 | 1 | 20 |
| K. pneumoniae, type A | | 1 | 4 | 7 | 4 | 1 | 1 | 1 | 1 | 20 |
| K. pneumoniae, type B | | | 9 | 5 | 4 | 1 | 1 | | 3 | 23 |
| K. pneumoniae, no type | | | | 1 | | | | | | 1 |
| P. vulgaris | 1 | | 5 | 9 | 38 | 22 | 5 | 4 | 1 | 85 |
| P. morganii var | | | 1 | 3 | 8 | 3 | 2 | 1 | 3 | 21 |
| Ps. aeruginosa | | | | 1 | 12 | 23 | 8 | 1 | 8 | 53 |
| Totals | 1 | 5 | 37 | 49 | 89 | 62 | 21 | 11 | 20 | 295 |
| Gram-positive organisms | | | | | | | | | | |
| Micrococcus | 1 | 1 | | | | | | | | 2 |
| Staph. albus | 2 | | | 1 | | | | | | 3 |
| Staph. aureus, hemolytic | 20 | 19 | 7 | 15 | 7 | 2 | 1 | 1 | 19 | 91 |
| Staph. aureus, non-hemolytic | 3 | 2 | 1 | | | | | | 2 | 8 |
| Hemolytic strep. beta, aerobic | 1 | | | 3 | 5 | 3 | | | 2 | 14 |
| Hemolytic strep. beta, microaero | 1 | 1 | 1 | | | | | | | 3 |
| Str. viridans, aerobic | | 4 | 2 | 3 | 8 | 6 | 3 | 1 | 6 | 33 |
| Str. viridans, microaero | | | | | | | | | 2 | 2 |
| Non-hemolytic strep., aerobic | 7 | | 2 | 12 | 9 | 19 | 4 | | | 53 |
| Non-hemolytic strep., microaero | | | | | | | 1 | | | 1 |
| Diphtheroids | 15 | 4 | 5 | | | | 1 | 1 | 15 | 41 |
| B. subtilis | | | 1 | | 2 | | | | | 3 |
| Totals | 50 | 31 | 19 | 34 | 31 | 30 | 10 | 3 | 46 | 254 |
| Grand totals | 51 | 36 | 56 | 83 | 120 | 92 | 31 | 14 | 66 | 549 |

Pulaski, Edward J.: Bulletin of U. S. Army Medical Department, November, 1946.

the bacteria tested (Table II) were destroyed by 32 units per cc. of streptomycin but even at higher concentrations some strains were not affected. Hirshfeld[15] found that with 256 units of streptomycin some strains were unaffected.

Thus, if penicillin were used alone the gram-negative bacteria would not be destroyed in the wound and they in turn would destroy penicillin; while if streptomycin were used alone all bacteria would not be destroyed and, moreover, some of the sensitive ones quickly become resistant.[14] For this reason, and because the flora of traumatic and clean-contaminated wounds always evolves through a mixture of gram-positive and gram-negative bacteria, even though one species may come to dominate the flora at one time, combinations of these antibiotics should always be used for topical applications.

Penicillin would have to be added fresh to the correct concentrations of streptomycin, however, because most varieties of penicillin rapidly lose potency on standing in solution. The solution of streptomycin is slightly acid, pH 5.6–6.5, and this acidity slowly destroys penicillin. The length of time that penicillin will maintain its strength in buffered streptomycin has not been determined. Because of these difficulties, it has been suggested that 5 per cent sulfamylon be used in place of penicillin. Ampules of this mixture will keep and can be sterilized. Sulfamylon is about as effective as penicillin;* it is non-toxic at this con-

* Penicillin is more powerful when the strains are susceptible.

centration, compatible with streptomycin, bactericidal and it acts quickly in the presence of pus. This concentration of sulfamylon and streptomycin encounters few resistant strains of bacteria. (Table III.)

TABLE III
STREPTOMYCIN 200 UNITS PER CC AND MARFANIL 5% AND 0.5% SODIUM BENZOATE

| Strain of Bacteria | Inhibition of growth of bacteria in area contacted by paper | Inhibition zone about this area |
|---|---|---|
| Staph | ++++ | ++ |
| Staph | ++++ | ++++ |
| Staph | | |
| Staph | ++++ | +++ |
| Staph | ++++ | +++ |
| Staph. and B. coli | ++++ | +++ |
| B. coli | ++++ | +++ |
| B. coli | ++++ | +++ |
| Proteus | ++++ | + |
| Proteus | ++++ | ++ |
| Pyocyaneus | ++++ | ++ |
| Pyocyaneus | ++++ | ++ |
| Hemolytic strep | ++++ | +++ |
| Green strep | ++++ | + |

Topical application of this mixture of antibacterials immediately places in the wound a higher concentration of these substances than could be obtained by parenteral therapy. As a result, a higher concentration is obtained sooner, by osmosis, inside tissues separated from blood supply. Parenteral therapy, for example, at best yields a blood concentration of 36 units of streptomycin and 30 units of penicillin while topical application can puddle in 200 units of penicillin or 200 units of streptomycin and 5 per cent sulfamylon, all within limits that do not interfere with the vitality of cells.

Tissues separated from blood supply in the wound always determine the issue as to infection. In the fresh wound, the tissue separated from blood supply is one of a triad with bacteria and foreign bodies that initiates infection. Although débridement removes dead tissue and foreign bodies and is successful thereby in preventing infection, complete débridement cannot always be accomplished nor can it always be done in time. Therefore, topically applied antibacterial substances provide the extra safety factor to prevent infection. In older wounds the tissues separated from blood supply that have not sloughed determine the chronicity of the infection.

The concentration of antibacterials in the tissues surrounding the wound differs according to circumstances. In the fresh wound, the vascular system in the surrounding tissues always leaches away and dilutes the antibacterial applied locally after a certain depth of penetration into the tissues. This leaching is greatest and occurs on the surface when there are young granulations present in the surrounding tissue. Leaching is least when there is local edema in the surrounding tissues, as occurs shortly after wounding. In general, an effective bactericidal level in the surrounding tissues is best maintained through parenteral therapy but a concentration can be obtained immediately and for a short period of time after wounding by injecting streptomycin and penicillin or sulfamylon of the correct concentration without causing harm locally. This superconcentration helps prevent infection and initiates parenteral therapy.

The following laboratory experiments will illustrate the effectiveness of this form of therapy. Crushed wounds were produced in the back of rabbits and contaminated with particular bacteria or with floor contamination. All developed infections in their wounds and up to 25 per cent of these animals died of septicemia. This mortality was reduced to zero by parenteral administration of penicillin and streptomycin and it was also reduced to zero by injecting 20 cc. of the mixture of streptomycin and sulfamylon in the tissues about the wounds after they were washed with the same solution.

FIG. 1. Infected wound; tissue crushed and contaminated five days before. Center is necrotic; profuse discharge of pus; direct smear made on blood plate shows many bacteria; wound definitely infected.

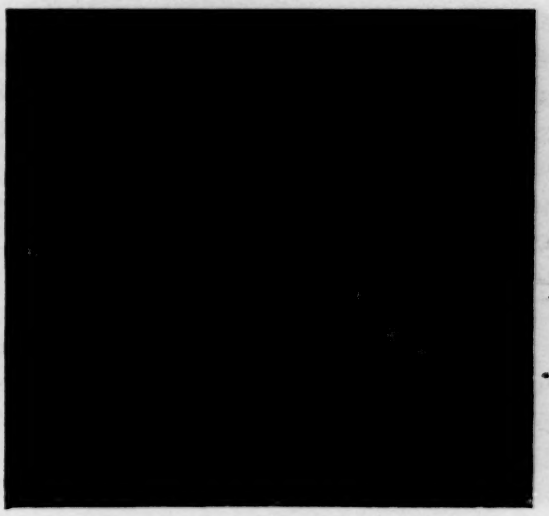

FIG. 2. Tissue crushed and contaminated five days before; however, this has been treated immediately by washing with mixture of streptomycin and sulfamylon. Surrounding tissues also injected with 20 cc. of mixture; no débridement of crushed tissue was carried out; the base of wound is filled with bright red granulations; there was no discharge of pus. Direct smear showed only occasional bacteria. The wound continued to heal without evidence of infection.

In these wounds the therapy was more effective in preventing infection than in shortening the resolution of established infection.[16] Moreover, infection was more easily prevented in fresh wounds than in those treated several hours after injury. Thus, infection was prevented in wounds treated immediately by washing and injecting the surrounding tissues with 20 cc. of streptomycin, 200 units per cc., and sulfamylon 5 per cent. (Figs. 1 and 2.) No attempt was made to débride the crushed tissue.

On the contrary, when the period between infliction of the wound and the time of therapy became greater than three hours, then the use of the mixture of antibacterials did not prevent infection unless the wound was freshened by débridement. With débridement and local chemotherapy, infection was prevented experimentally as late as forty-eight hours after wounding. The time limits when this combined therapy will no longer be effective have not been determined. Neither has the effectiveness of the mixture of sulfamylon and streptomycin been investigated as to its capacity to decontaminate wounds before delayed primary suture is carried out.

Despite the success of the immediate use of this mixture of streptomycin to prevent infection experimentally in crushed wounds, no attempt should be made to treat traumatic wounds with it unless the wound is first carefully débrided. These experimental wounds, unlike traumatic wounds, did not contain foreign bodies. On the other hand, as has already been mentioned, because all injured tissue cannot always be débrided from traumatic wounds and because the procedure cannot always be carried out early, employment of the combination of streptomycin and sulfamylon or penicillin locally at the time of the débridement will definitely help to prevent infection.

Clinically heavily contaminated operative wounds have been washed immediately with this combination of antibacterials and infection prevented. These wounds, that are made clean and then contaminated,

contain a minimal amount of crushed tissue and foreign bodies, and in them the immediate use of the antibacterial combination corresponds to its use in experimental wounds. In other words, this mixture is a subcutaneous antiseptic—a therapeutic ideal that has been sort for a long time. Its topical use can be highly recommended in surgery of the large bowel and of hemorrhoids.

Why the mixture of streptomycin and sulfamylon failed to work in crushed contaminated wounds three hours after infliction is interesting because the failure of antibacterials and antibiotics to hasten the resolution of the established infection has, in part at least, the same etiology. After three hours the bacteria were found to be just as susceptible to the action of the antibacterials; actually they were fewer in number and contact with them should have been as effective because the solution was injected in both instances. Fibrin was deposited in the injured tissues, of course, and microscopic examination disclosed that many of the bacteria had entered leukocytes. The latter seems to be the most important change because the bacteria were now in a position where the solution could not reach them unless the leukocytes were destroyed or until the bacteria were again freed from the leukocytes. Bacteria freed from leukocytes and not destroyed would be capable of re-initiating infection.

To hasten resolution of the localized established infection, an adjunct chemical substance is definitely needed to implement the action of antibacterial substances. This type of infection invariably subsides promptly when all devitalized tissues disappear from the wounded area and it persists as long as these sloughs are present. Fascias and bone are not readily liquefied by tissue enzymes and their persistence accounts for the chronicity of infection in wounds containing sloughing fascia and in osteomyelitis. To aid in the liquefaction of fascia and to explode leukocytes containing bacteria, as well as to limit mold growth that inhibits enzymatic digestion, a mixture of acid, glycerine and thymol has been used to clear the wound of puddles of pus and small pieces of slough that cannot be removed with scissors. The acid-glycerine-thymol combination is puddled into the wound and kept there for approximately three hours. This exposure also causes a very slight erythema, the granulations become bright red and they sometimes bleed slightly. The acid is then washed from the wound because it tends to destroy streptomycin and fine mesh gauze saturated with the combination of streptomycin and sulfamylon or penicillin is packed into it. The procedure is carried out daily until the infection disappears. In chronically established local infections where bone is not involved, rapid resolution has been obtained. The amount of drainage decreases within forty-eight to sixty-four hours and granulations soon begin to fill the wound. On the other hand, when osteomyelitis is present, particularly if pyocyaneus is in the flora, only temporary improvement is obtained and then the infection continues although the discharge of pus is less and is better managed. Pulaski[14] has likewise reported the failure of streptomycin to resolve infection in wounds complicated by osteitis.

Persistent gram-negative infections in wounds that are not maintained by the presence of sloughing tissues have been eliminated by the local use of streptomycin. White,[7] for example, has reported that amputation stumps that would not take skin grafts because of the presence of gram-negative bacteria were, in many instances, cleared of infection and thereafter the grafts took successfully.

Streptomycin has been used topically in the rectum for inflammatory disease, particularly for ulcerative colitis. The number

of cases is still too few to judge the efficacy of this form of treatment. Faget* has reported that streptomycin applied as wet dressings and in an ointment has healed indolent ulcers on the legs of lepers. The nature of the proper ointment base to use with streptomycin for topical therapy has not been worked out. Such an ointment should be useful in treating diseases of the perineal region.

## SUMMARY

1. For topical application to wounds, a solution of streptomycin of the proper concentration should be used, not the powder. Freshly wounded tissues are not damaged further and wounds heal without interference when the concentration of streptomycin is at 200 units or micrograms per cc. Granulations are not damaged by 1,000 units per cc. At these concentrations, streptomycin is the best non-toxic antibiotic that has been found to date for gram-negative bacilli.

2. Penicillin, up to 1,000 units, or sulfamylon 5 per cent should always be combined with streptomycin when it is used topically because streptomycin does not have a complete bacterial spectrum at its proper concentration and some susceptible bacteria rapidly acquire resistance to streptomycin alone.

3. Conversely, streptomycin should always be used topically with penicillin because streptomycin kills gram-negative bacilli that penicillin is unable to destroy and these elaborate penicillinase that in turn destroys penicillin.

4. Gram-negative bacilli are almost always present at some time in the evolution of the bacterial flora of wounds even though only a single strain of bacteria may be isolated at one time. Gram-negative bacilli usually dominate the flora of chronically infected wounds, accounting in part for the failure of topical application of penicillin alone in this type of wound.

5. Gram-negative bacilli definitely interfere with the healing of wounds despite arguments that have been advanced that they are mere contaminants of pus.

6. Because of its stability, sulfamylon 5 per cent makes a better combination with streptomycin than with penicillin. Sulfamylon has a wider bacterial spectrum than penicillin though it is not always as powerful and it acts rapidly in the presence of pus. It can be used with any form of parenteral therapy. This mixture encounters few resistant strains of bacteria.

7. Topically, the solution of streptomycin and penicillin or sulfamylon will prevent infection in wounds better than it will hasten the resolution of established infection, except in certain instances in which no slough is present.

8. In the presence of crushed tissue, prevention of infection can be obtained experimentally until three hours after wounding by washing the wound and injecting about 20 cc. of the solution in the surrounding tissues. With débridement of crushed tissue, prevention of infection has been effected as late as forty-eight hours after wounding when the solution is employed in the same manner.

9. All devitalized tissue cannot be débrided from traumatic wounds nor can the process always be done in time; therefore, topical application of the solution of streptomycin and penicillin or sulfamylon is recommended in the treatment of traumatic wounds as a safety factor to prevent infection.

10. The solution of streptomycin and penicillin or sulfamylon will decontaminate the clean-contaminated operative wound. The solution is applied topically before the wound is closed as one would an antiseptic to the skin.

* Faget, G. H. Research in Antibiotics Symposium. Washington, D. C. January 31–February 1, 1947.

11. To hasten resolution of the established localized infection in the wound, adjunct chemotherapy in addition to antibacterial chemotherapy is required. This adjunct chemotherapy must liquefy slough and cause the antibacterial substances to penetrate and kill bacteria in slough and leukocytes.

12. A mixture of acid, glycerine and thymol has been used for this adjunct chemotherapy. It is successful when sloughing fascia is present but it is not successful in the presence of osteomyelitis.

13. Streptomycin alone can rid wounds of persistent gram-negative bacilli infection when no slough is present in the wound. For example, granulations that will not take skin grafts because they harbor a flora of the gram-negative bacilli can be freed of these bacteria by the local application of streptomycin and then skin grafts will take.

14. No otic complications have been observed with the low concentration of streptomycin used topically. However, topical therapy has not been used as frequently nor over such long periods of time as parenteral therapy.

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# The Present Status of Treatment for Influenzal Meningitis*

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THERE are now available three effective antibacterial agents for treatment of type b H. influenzae infections: sulfadiazine, type b H. influenzae rabbit antiserum and streptomycin. It is already evident that each one when used separately is limited in its curative effect in severe infections. On the other hand under certain circumstances each one can bring about recovery. Evaluation of the separate action of each has become increasingly difficult the greater the number of agents available. This paper will present the results of our attempt over the past ten years to assess the efficiency of each of these therapeutic agents and the indications for their use.

## COMBINED ACTION OF SULFADIAZINE AND TYPE b H. INFLUENZAE RABBIT ANTISERUM

At the beginning the high mortality in influenzal meningitis, over 90 per cent, justified the use of all potentially effective agents. The combined action of sulfonamides and rabbit antiserum specific for type b H. influenzae* has been used at Babies Hospital for the treatment of meningitis since 1938. This therapeutic program has been simplified and made more efficient by the application of certain principles. The dose of antibody needed varies with the severity of infection. Therefore, some objective criterion of severity is essential. Moreover the sufficiency of the original dose decided upon requires confirmation.

1. The best index of severity of infection proved to be concentration of sugar in the spinal fluid withdrawn before treatment; the lower the concentration, the greater the severity.

2. Heidelberger[1] showed that the antibody in the rabbit antiserum could be measured by the quantitative chemical method for determining agglutinin and precipitin nitrogen. Mouse protection tests showed that the protective element in the antiserum was actually the anticarbohydrate antibody which this method measured in mg. of antibody nitrogen per cc. Thus it was possible to formulate a quantitative approach to treatment as shown in Table I.

TABLE I
SCHEDULE OF DOSAGE ON SPINAL FLUID SUGAR

| Spinal Fluid Sugar (Mg. per cent) | Mg. Antibody Nitrogen Indicated |
|---|---|
| 15 | 100 |
| 15 to 25 | 75 |
| 25 to 40 | 50 |
| over 40 | 25 |

3. This plan aimed to introduce at one time the amount of antibody necessary for recovery. Nevertheless, it was necessary to check its sufficiency. The capsular swelling capacity of the patient's serum following treatment proved to be a good guide. This test was performed daily through the period of activity of infection; and unless it could be shown that the patient's serum contained an excess of free antibody sufficient to cause

* H. influenzae type b rabbit antiserum used in this study was supplied by E. R. Squibb and Sons.

* From the Babies Hospital and the Department of Pediatrics, Columbia University College of Physicians and Surgeons, New York. The work reported in this communication was supported by grants from the Commonwealth Fund.

capsular swelling of the organisms when diluted 1:10, another dose of antiserum was administered (25 to 50 mg.).

The therapeutic program just described was greatly simplified when it was learned that prompt recovery followed introduction of this antiserum by the intravenous route only. In a given case sodium sulfadiazine is introduced by the subcutaneous route in a quantity equivalent to 0.1 Gm. per Kg. as soon as diagnosis of type b H. influenzae is made. A continuous intravenous drip is set up immediately if there is urgent need of fluids and 5 per cent glucose in saline (approximately 30 cc. per Kg.) is administered over the next hour. Then the quantity of antibody, calculated according to Table I, is diluted in 10 cc. per Kg. of physiologic saline and added to the reservoir of continuous drip apparatus. The speed is so regulated that the diluted antibody will be administered in two hours. The antiserum may be given by the intramuscular route when necessary; however, in our limited experience a larger total quantity is needed when this route is used. Sulfadiazine is given orally as soon as feasible and continued for seven days after the first sterile spinal fluid is obtained. No additional serum is given unless the capsular swelling test shows inadequate excess of antibody in the patient's serum.

When patients are treated early with the combined therapy of sulfadiazine and type-specific rabbit antibody according to the principles outlined,[2] the response has been so consistent that it is possible to predict not only the outcome but the course of recovery. Even in the fulminating group in which the meningitis progresses so rapidly that the spinal fluid sugar falls to less than 15 mg. per cent within twenty-four hours of onset, prompt recovery can be expected in all cases if sufficient antibody is administered in the initial dose. Actually only 80 per cent of the ninety patients treated according to this regimen recovered, the failures being attributable to delay in diagnosis and to unwarranted confidence in the value of sulfonamides alone.

## SULFONAMIDES

The limitations of sulfonamides as therapeutic agents in influenzal meningitis are now well established. Nevertheless, it is clear that a certain proportion of patients do recover on sulfonamides alone. Our own clinical experience suggests that this fraction is small and we are inclined to believe that the published records of isolated examples of cure with sulfonamides alone convey a false optimism as to the true efficacy of these agents. Over one-fourth of our patients received serum only after extended periods of unsuccessful sulfonamide therapy in other hospitals. Only two-thirds of this group recovered when serum was added; in virtually all of these the infection had been kept under control during treatment but had not been eliminated, for on withdrawal of the drugs recrudescence occurred. This experience led us to study the criteria for selecting those patients who might be expected to recover on sulfonamides alone, and for this purpose we made a comparison of the protective value in mice of available sulfonamides alone, antiserum alone and the best sulfonamide and serum in conjunction. The results established the fact that the efficiency of sulfadiazine, the most effective of three sulfonamides tried, was dependent upon the size of the bacterial population whether in the test tube or mouse and suggested that it might be able to cure meningitis if used early in mild infections. Whereas the protection with sulfonamide alone never exceeded 10,000 M.L.D., when serum was added the mice withstood 1,000,000 M.L.D.[3]

These observations resulted in the adoption of certain criteria for selection of patients who might be expected to recover on sulfadiazine alone. When meningitis has

been present for only twenty-four hours, the infection is judged mild, as indicated by a concentration of sugar in the spinal fluid of 40 mg. or more per 100 cc., and when the clinical features are in keeping with this, the use of sulfadiazine alone is justified initially. If *in vitro* tests indicate usual sensitivity of strain, it is believed that the drug alone may be continued without risk, provided clinical improvement ensues and provided the spinal fluid shows the infection to be under control, with cultures sterile forty-eight hours after the start of chemotherapy. A minimum of two weeks of such treatment is essential for elimination of infection. It is of interest that during a period when approximately thirty patients were treated only two fulfilled the criteria which justified the use of sulfonamides alone. Reports of visiting physicians from Europe indicate that the present mortality rate there in influenzal meningitis is 75 per cent; sulfonamides are the only available therapeutic agents.

TABLE II
SUMMARY OF PROTECTIVE POWER OF THERAPEUTIC AGENTS IN MICE

| Therapeutic Agent | Protection | |
|---|---|---|
| | M.L.D. | No. of Mice |
| Sulfanilamide | 500 | 120 |
| Sulfadiazine | 9,250 | 280 |
| Type b rabbit antiserum | 28,875 | 625 |
| Sulfadiazine + serum | 1,000,000 | 270 |
| Streptomycin | 100,000,000 | 200 |

It must be emphasized that these therapeutic recommendations refer only to meningitis. Experience with the other varieties of severe infections caused by H. influenzae, pneumonia, obstructive infections of the respiratory tract, arthritis, etc., is much less extensive but certain facts are clear. Sulfadiazine alone constitutes an effective treatment for H. influenzae pneumonia in older children. The characteristic clinical syndrome of H. influenzae epiglottitis, causing respiratory obstruction, responds promptly to sulfadiazine alone in the majority of patients after tracheotomy.[4] When H. influenzae produces pyarthrosis and osteomyelitis, the possibility of injury to epiphysis and cartilage is so great that treatment should aim for the most rapid termination of infection. This is best accomplished by the simultaneous use of all effective therapeutic agents.

### STREPTOMYCIN

The demonstration by Waksman[5] and other investigators[6] of the antibacterial action of streptomycin on other gram-negative bacilli naturally led to its trial against H. influenzae. Investigations were carried out first in the laboratory.[7,8] *In vitro* sensitivity of a number of strains was studied by determining the lowest concentrations of streptomycin which when incorporated in Levinthal agar could completely prevent growth of inocula averaging 700 million organisms after an incubation period of forty-eight hours. All strains tested before exposure to streptomycin were completely prevented from growing by 7.5 units per cc. save for one or two colonies which grew in some tests on an occasional strain on 10 and 13 units per cc.[8,9] *In vivo* the sensitivity was also very great. A single dose of 20 to 80 units per mouse protected mice regularly against more than 1,000,000 M.L.D. (minimal lethal doses); larger doses were effective against 100,000,000 M.L.D. Table II lists for comparison the protective values of the various available therapeutic agents. It is seen that streptomycin's protective power exceeds that of any other single agent and even the combined action of specific rabbit antibody and sulfadiazine. It has been demonstrated that streptomycin actually exerts a rapid lethal action on H. influenzae.[10]

After demonstrating the rapid lethal injury resulting from the action of streptomycin on type b H. influenzae, *in vitro* and in the mouse, we were naturally led to explore its therapeutic value in influenzal meningitis. Investigation of the separate action of streptomycin in these patients was difficult for two reasons; first, because most of the patients had already received sulfonamides for a period long enough to reduce the bacterial population, and also because there was already available a treatment which had been shown to be capable of curing virtually 100 per cent of the patients when applied according to certain principles in the first few days of the disease. I refer to the combined action of type specific rabbit antiserum and sulfadiazine. Nevertheless, this trial was considered necessary because if found equally effective, streptomycin could be expected to possess certain advantages over the earlier therapeutic program. Serum sickness could be eliminated. Streptomycin has been shown to be active against all six types of encapsulated H. influenzae as well as the non-encapsulated, non-typable variety of this organism which occasionally causes subacute bacterial endocarditis in adults and meningitis in very young infants. This is true of sulfadiazine also but type b H. influenzae antiserum, the only therapeutic serum available at present, is effective only against type b. However, over 95 per cent of all serious infections caused by the group are due to type b.

*Schedule and Dosage.* Using the dose previously found safe in adults and in a few children treated at Babies Hospital, 20,000 units per pound or 44,000 units per Kg. each twenty-four hours, blood concentrations were determined during two methods of intramuscular administration, by continuous drip and by injections at intervals of three hours. The range of concentrations found is listed in Table III; it is seen that they are sufficient for prevention of growth of inocula averaging 700 million organisms if the results obtained *in vitro* can be applied to the influence of streptomycin on bacteria in the patient. With the exception of the cases reported[11] all patients have been treated by interrupted intramuscular injections at three-hour intervals. The experience of other investigators and our own agree that in meningitis streptomycin must be administered intrathecally; the concentrations present in the spinal fluid after intramuscular use are not adequate. A dose varying from 25,000 to 50,000 units has been introduced daily into the lumbar subarachnoid space. More recently, the first two

TABLE III

VARIATION IN CONCENTRATION OF STREPTOMYCIN BLOOD AND SPINAL FLUID COMPARED WITH MINIMAL EFFECTIVE CONCENTRATION

| Case | Concentrations of Streptomycin Units per cc. | | Dose and Route of Streptomycin Units in 1,000's | | | M.E.C.[1] Units per cc. |
|---|---|---|---|---|---|---|
| | Blood* | Spinal Fluid† | I.M. | Each 24 Hours | I.T. | |
| 1 | 8.9–30.6 | 9.1–20.4 | C.D. | 20,000‡ | 50 | 2.7 |
| 2 | 5.1–10.1 | ..... | q3h | 20,000 | 25 | 2.6 |
| 3 | 4.2– 8.5 | 5.1–11.5 | q3h | 20,000 | 25 | 4.9 |
| 4 | 10.1–19.1 | 11.8–20.0 | q3h | 20,000 | 25 | 1.6 |
| 5 | 6.2–14.6 | 6.2– 6.0 | q3h | 20,000 | 50 | 2.8 |
| 6 | 5.5–14.5 | 5.0–28.0 | q3h | 20,000 | 25 | 2.8 |
| 7 | 3.3– 6.5 | 8.5– | q3h | 20,000 | 25 | 4.4 |
| 8 | 7.3–22.0 | 4.9–16.3 | q3h | 20,000 | 30 | 7.5 |
| 10 | 5.8–12.2 | 5.1–12.1 | C.D. | 20,000 | 50 | 2.5 |
| 11 | 9.3–10.5 | 9.3– 9.6 | q3h | 20,000 | 25 | 1.6 |
| 12 | 7.5– 9.8 | 11.1– | q3h | 20,000 | 25 | 4.4 |

* Specimen collected at random when intramuscular dose was given by continuous intramuscular drip. When streptomycin was given every three hours the blood was withdrawn three hours after the last dose.

† Spinal fluid concentrations represent those found twenty-four hours after intrathecal dose listed.

I.M., intramuscular; I.T., intrathecal; M.E.C. minimal effective concentration; C.D., continuous intramuscular drip; q3h, every three hours.

‡ Units per pound (0.5 Kg.).

[1] M.E.C., minimal effective concentration of streptomycin necessary to completely prevent growth on Levinthal agar in forty-eight hours when inoculum represents loop from growth on Levinthal agar after six hours' incubation.

intrathecal doses have been given at twelve-hour intervals and 25,000 units have been used as the intrathecal dose in children under three years. There is ample evidence that four to five days of this treatment is sufficient. What streptomycin has failed to accomplish by this time will not be likely to occur after longer periods. If the culture continues to grow, the addition of other therapeutic agents is indicated. The occurrence of eighth nerve deafness and labyrinth dysfunction in a significant number of patients treated for periods longer than one week makes it a serious responsibility to reduce treatment to a minimum.

During the past two years three different therapeutic programs have been used. The changes have resulted from clinical experience as well as experimental results on the action of streptomycin on type b H. influenzae.

*Results of Treatment.* In the first twelve patients, treated according to our first program, streptomycin was used as the only therapeutic agent after admission to Babies Hospital unless it became evident from the poor response that amplification of this treatment was indicated. However, all patients with the exception of No. 12 had previously received sulfadiazine. All of the patients received streptomycin alone either throughout the period of treatment or for four days before the addition of other agents. From analysis of this group it is evident that recovery was prompt in the eight patients in whom the infection was mild or moderately severe, as judged by the concentration of sugar in the spinal fluid before treatment, as well as by clinical signs. On the other hand those with severe meningitis were not cured with streptomycin.

In three of these patients in whom streptomycin failed physical signs of chronic meningitis were present, and the concentrations of sugar in the spinal fluid were below 15 mg. per 100 cc. The prognosis for complete recovery would be uncertain under any known treatment regimen. The disease of the fourth patient (case 12) in this group ran a fulminating course, since he was reported to have been up and well twenty-four hours prior to the institution of streptomycin therapy. On admission he was in a semicomatose state and the level of sugar in his spinal fluid was only 6 mg. per cent. In our experience, such a patient could be expected to recover promptly under treatment with rabbit antiserum and sulfadiazine in adequate quantities. In two of these patients the unsatisfactory response led to the addition of type specific antiserum after four days of streptomycin treatment. In only one of these, case 12, was H. influenzae cultivated from the spinal fluid at the time antiserum was added, but in the other the worsening of the clinical condition and persistence of a low concentration of sugar in the spinal fluid demanded the use of additional therapy. In case 12, in which infection was early, H. influenzae was grown from all specimens of spinal fluid withdrawn during streptomycin administration. The organism cultivated from the spinal fluid twenty-four hours after the initiation of treatment with this antibiotic was found to be resistant to 1,000 units of streptomycin per cc.; 100 per cent of the bacterial population showed this degree of resistance. After the addition of antiserum and sulfadiazine, recovery was prompt and complete. The other patient, who received antiserum and sulfadiazine after four days of streptomycin therapy, exhibited evidence of serious cerebral damage. The two patients who were treated with streptomycin without additional therapy succumbed to the infection. In one the infection continued because the organisms which persisted were resistant to streptomycin. The other patient appeared to be improving by clinical standards; the spinal fluid became sterile and its chemical constituents normal. At necropsy a large

subarachnoid abscess containing H. influenzae was found.

The failure of streptomycin alone to cure any of the four patients with severe meningitis led to the second change in our therapeutic program. Only patients with initial spinal fluid sugar concentrations significantly above 15 mg. per cent were to receive streptomycin alone; those with concentrations at or below this level would receive all three therapeutic agents, streptomycin, sulfadiazine and specific rabbit antiserum initially. This therapeutic program has proved successful.

Table IV summarizes our results, already reported, of treatment* of the first twenty-five patients.[11] In twelve patients already discussed the first therapeutic program was followed and in subsequent severe infections plan two was instituted. A larger experience continues to show prompt and complete recovery following use of streptomycin alone in those patients whose original spinal fluid sugar concentrations are significantly above 15 mg. per cent.

TABLE IV
SUMMARY OF TREATMENT OF TWENTY-FIVE PATIENTS

| No Patients Treated | Severity of Infection | S.M. Alone | | | Serum after 4 Days of S.M. | | | S.M. after Unsuccessful Serum and Sulfa | | | S.M. Serum Sulfa Initially | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | R | S | D | R | S | D | R | S | D | R | S | D |
| 13 | Mild or average | 12 | .. | .. | .. | .. | .. | 1 | | | | | |
| 8 | Severe chronic | .. | .. | 2 | .. | 2 | .. | 1 | 1 | 1 | 1 | | |
| 4 | Severe early | .. | .. | .. | 1 | .. | .. | .. | .. | .. | 3 | | |

S.M. = Streptomycin
R = Recovered
S = Survived
D = Died

Total R S D
19 3 3

*Origin and Nature of Resistant Type b H. Influenzae to Streptomycin.* The proof that emergence of resistance of the strain was the cause of failure in two of these patients and in one patient with epiglottitis and bacteremia due to this organism, led to a study of the mechanism of resistance.

In order to explain these failures the strains isolated before streptomycin therapy from ten of these patients, treated according to first therapeutic program, were studied for evidence of fundamental differences between the group from patients in whom streptomycin failed and those from the patients who were promptly cured. In addition experiments were designed to determine the origin and nature of the resistant organisms which made up either 100 per cent or an appreciable part of the population grown from three of these patients during unsuccessful streptomycin therapy.

The routine *in vitro* sensitivity tests, which examined populations varying approximately from 1 million to 1,700 million organisms, failed to reveal a significant difference among the strains isolated from these ten patients prior to streptomycin treatment. Moreover infections produced in mice with the original strains, which later became resistant in patients during streptomycin treatment, exhibited marked sensitivity to streptomycin action. While neither the standard *in vitro* sensitivity test nor the mouse test applied to the cultures isolated before treatment of the patients with streptomycin could detect a difference between the strains from cases in which streptomycin was promptly effective and those from patients in whom resistance of the strain developed, when these procedures were applied to the same strains which continued to grow from the spinal fluid after treatment, they served as a good index of efficiency of treatment. Growth was easily demonstrable in 1,000 units of streptomycin per cc. and it was impossible to protect mice against such modified strains with doses as high as 5,000 units per mouse.

Therefore, enormous populations of each of the ten strains (142 to 522 billion) were

* The streptomycin used for treatment of patients and experimental studies was supplied by E. R. Squibb and Sons.

examined by a procedure which could demonstrate the presence, even in very small numbers, of organisms resistant to 1,000 units of streptomycin per cc. Certain factors learned from patients in whom streptomycin failed directed us to this approach. When emergence of resistance of the strain was responsible for therapeutic failure a relatively small inoculum of the culture from the spinal fluid grew on Levinthal agar containing 1,000 units per cc. of streptomycin. In one patient 100 per cent of the population of the culture grown from the spinal fluid withdrawn twenty-four hours after beginning streptomycin therapy, showed resistance to 1,000 units per cc. This concentration was so rapidly bactericidal for sensitive organisms *in vitro* that it was possible to examine 15 to 30 billion organisms in each pour plate of Levinthal agar containing 1,000 units of streptomycin per cc. without inhibiting growth of the resistant organisms as a result of accumulation of end products of bacterial metabolism; sensitive organisms were killed before they had a chance to reproduce. All colonies growing under these circumstances were resistant to 1,000 units of streptomycin per cc. The details of the test have been reported.[9] Table v lists the results of the ten strains.

Strains, 1, 2 and 3 were isolated from patients in whom streptomycin therapy failed because of emergence of resistance of the strain. The organisms grown from these patients before streptomycin therapy were sensitive according to conventional methods, whereas after a period of treatment of one, twenty-one, and three days, respectively, they grew in a concentration of streptomycin of 1,000 units per cc. Strain 4 was cultivated from a patient who improved at first and whose spinal fluid became sterile and normal by all standards but who died from pressure changes secondary to a large subdural abscess. The other six strains were grown from spinal fluid of patients who were cured promptly by streptomycin. Again it should be emphasized that the tests described were applied in all instances to cultures isolated from patients before the start of streptomycin therapy.

TABLE V

INCIDENCE OF RESISTANT SURVIVALS IN LARGE BACTERIAL POPULATIONS SEEDED IN LEVINTHAL AGAR CONTAINING 1,000 UNITS OF STREPTOMYCIN PER CC.

| Patient and Strain | Total Organisms Examined, Billions | Organisms Examined Per Plate, Billions | Colonies Total Survival | *Incidence of Resistant Colonies | Clinical Results |
|---|---|---|---|---|---|
| 1. | 381 | 25.4 | 57 | 1:6.7 billion | Failure |
| 2. | 142 | 14.2 | 23 | 1:6.2 billion | Failure |
| 3. | 301 | 30.1 | 26 | 1:11.5 billion | Failure |
| 4. | 423 | 29.2 | 32 | 1:13.2 billion | Failure |
| 5. | 253 | 25.3 | 20 | 1:12.6 billion | Recovered |
| 6. | 522 | 34.8 | 474 | 1:1.1 billion | Recovered |
| 7. | 188 | 18.8 | 18 | 1:10.4 billion | Recovered |
| 8. | 256 | 25.6 | 172 | 1:1.5 billion | Recovered |
| 9. | 166 | 16.6 | 12 | 1:13.8 billion | Recovered |
| 10. | 284 | 28.4 | 37 | 1:7.7 billion | Recovered |

* Ratio of resistant colonies to total population cultures.

It is seen that all ten cultures studied before exposure to streptomycin contain a minute fraction of members (expressed by the ratios in the column "Incidence of Resistant Colonies") which can grow in the presence of 1,000 units per cc. of the antibiotic. These ratios seem to bear no relationship to the tendency exhibited by a strain to emerge resistant during treatment of the patient. In fact, two of the strains, Nos. 6 and 8, cultivated from patients in whom streptomycin was promptly successful in eliminating the infection, showed a greater prevalence of resistant members than those which later emerged resistant during treatment.

The results demonstrate that the emergence of resistance is a selective process; the

sensitive members are killed, permitting the resistant organisms to declare themselves. When patients are treated according to the program described the size of the bacterial population is the most important single factor among those which determine the potentialities of a strain to exhibit this degree of resistance during treatment of a patient or in the test tube. However, when streptomycin is administered only by the intramuscular route, relatively small populations in the spinal fluid, when exposed to the low concentrations of streptomycin which are present in spinal fluid, will exhibit resistance of a significant but lesser degree.

These resistant variants apparently present in large populations of all sensitive strains of H. influenzae have been proven to originate from mutations.[12] Therefore, we can expect the continuous random occurrence of resistant mutants in patients if the disease is sufficiently severe or, in other words, if the bacterial population is large enough. The rate of occurrence of the resistant mutants did not differ significantly among the ten strains.[12] Therefore, the emergence of resistance of the strains in the three patients in whom streptomycin failed, cannot be explained on a greater frequency of occurrence of mutations. The resistant trait is transmitted unchanged in degree through many generations. Therefore, the appearance of a few mutants in a patient during treatment can lead to a serious infection which is uninfluenced by streptomycin. Moreover the persistence of resistant organisms in the nasopharynx of patients whose strains emerged resistant during streptomycin treatment constitutes a significant public health problem. In one streptomycin-treated patient followed at intervals for one year after recovery from meningitis all of the cultures of H. influenzae isolated from his nasopharynx showed resistance to 1,000 units of streptomycin per cc.

A fraction of the mutants which are resistant to streptomycin exhibit nutritional requirements different from the parent strain. There are even different nutritional needs among members of this minority. The results suggest that some may differ so greatly from the parent strain that normal Levinthal agar, an ideal medium for the majority group, is inadequate for their growth. This raises the question whether our failure to grow organisms from some patients is explained on a nutritional basis. Three patients with severe meningitis treated with streptomycin alone failed to improve clinically, the concentration of sugar in the spinal fluid remained low and in one a large number of gram-negative bacilli were seen on stained smear, but the cultures showed no growth. Following the institution of rabbit antiserum and sulfadiazine recovery was prompt.

It is of great significance therapeutically that the mutants, resistant to streptomycin,[13] are in general sensitive to sulfadiazine. As a result of this evidence our third therapeutic policy was instituted. Except for infants under six or seven months of age, patients with signs of severe meningitis are now treated with sulfadiazine and streptomycin. Those with milder disease will continue to receive streptomycin alone; the young infants with severe meningitis will receive all three therapeutic agents, streptomycin, sulfadiazine and specific rabbit antiserum. Three patients with manifestations of severe meningitis have been successfully treated with sulfadiazine and streptomycin used simultaneously from the beginning.

## SUMMARY

A larger experience and more time for long term evaluation of physical and mental development are needed before final statements can be made concerning the results of treatment of H. influenzae infections. Certain facts are evident, however.

In patients in whom the infection is mild or moderately severe, according to the criteria previously described, either streptomycin alone or sulfadiazine in conjunction with specific rabbit antiserum can be expected to cure 100 per cent of them. A small fraction can be cured by sulfadiazine alone.

When manifestions of severe infection are present in patients in whom it is evident from the history that the onset of the meningitis can be dated within a few days, the results suggest that a choice may be made between two therapeutic programs, the combined action of sulfadiazine with either streptomycin or type b H. influenzae antiserum. Experience with the latter regimen is so extensive that one can predict complete recovery in virtually 100 per cent of these patients. The use of the former program, simultaneous use of sulfadiazine and streptomycin, is still too limited to recommend it with assurance in this group, though its success is anticipated. Patients whose infections have progressed to the severe state despite the use of sulfonamides cannot be considered suitable cases for treatment with sulfadiazine in conjunction with streptomycin; the presence of sulfadiazine resistant H. influenzae in significant numbers may prevent these agents from eliminating the meningeal infection. Moreover a longer period of study on the toxic effect of streptomycin on the central nervous system is necessary before it can be recommended as the treatment of choice for this group even if it proves to be equally effective.

Those patients with severe meningitis and a history which suggests that uncontrolled meningitis has been present for a week or more or who show signs of chronic meningitis with or without manifestations of localized cerebral injury should receive sulfadiazine, streptomycin and specific rabbit antiserum simultaneously. The latter program can be expected to reduce the risk of failure to a minimum since it combines the action of three antibacterial agents which exert their destructive influences through three different mechanisms. Members of the population resistant to one can be attacked by another or both the others. The difficulty in determining the time of onset of meningitis in young infants under seven months of age, because of failure of these infants to exhibit signs of meningeal infection until several days after onset, together with the still high mortality rate in this group, have led us to recommend the use of sulfadiazine, streptomycin and specific rabbit serum initially for these infants. It is in this severest group that the addition of streptomycin to sulfadiazine and specific antiserum can be expected to reduce the 20 per cent mortality which resulted from the combined use of the last two agents.

The use of streptomycin alone or in conjunction with sulfadiazine is justifiable only when laboratory facilities permit evaluation of severity of infection and progress of recovery. The need for bacteriologic methods which can detect small numbers of viable organisms and evaluate sensitivity of any culture grown from the spinal fluid, is of paramount importance.

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# Treatment of Tularemia with Streptomycin*

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STREPTOMYCIN approximates the ideal therapeutic agent for tularemia. Multiplication of *Bacterium tularense* is prevented by a drug concentration of 0.4 microgram per cc., and the average virulent strain is killed *in vitro* by exposures to concentrations of 0.4 $\gamma$/cc. for two hours, of 1 $\gamma$/cc. for thirty minutes, and of 2 $\gamma$/cc. for eight minutes.[3] This high degree of sensitivity of the causative agent to the antibiotic permits effective therapy of the experimental disease caused by 10 to 100 multiples of the MLD in totally non-resistant rodents. In addition to Heilman's[1] report there are other excellent, and somewhat more quantitative, studies on streptomycin therapy of the experimental disease, performed during the war, that are either unpublished at this time or available only in abstract. This is unfortunate, for only those who are familiar with these or similar data can realize how little streptomycin is required to prevent certain death in highly susceptible and wholly non-resistant animals.

Single doses of 10 $\gamma$/Gm. body weight protected 92 per cent of mice against simultaneous challenge with 15 to 20 MLD of a strain of maximal virulence. When therapy was delayed for seventy-two hours after this challenge dose the minimal quantity which effected 80 per cent survival was 10 $\gamma$/Gm. every three hours for ten days.[2] For comparison, a calculation from data presented in Heilman's first protection test shows that approximately 7 $\gamma$/Gm. every three hours for ten days protected all of fifteen mice when therapy was delayed for seven hours after challenge with 32 $LD_{50}$ doses. In other work the total $ED_{50}$ dose (median effective dose, sparing 50 per cent of all animals) administered in four equal portions every two hours, the first portion at time of challenge with 50 $LD_{50}$ doses of the same virulent strain, averaged 350$\gamma$ for the 20 Gm. mouse, or 17 $\gamma$/Gm.[3]

The implications in the above, and in other similar data, seem reasonably clear that streptomycin therapy of tularemia in man should be at least as effective, if not more so, at equivalent concentrations and administrative periods than it is in mice, hamsters, and guinea pigs whose recoveries are solely dependent upon streptomycin alone, for the average human develops so great a degree of natural resistance after infection that clinical and histologic aspects of the disease soon exhibit subacuteness and chronicity, and the mortality rate is characteristically low, averaging about 6 per cent. The purpose here is to learn by examination of available clinical data how well the early collective experience has kept pace with expectations.

Quantitative information about the results of therapy was obtained from thirty-seven patients, including one that died, giving a fatality rate of 2.7 per cent for the series. The items of importance in the composition of the group are an average age of thirty-six with extremes of ten and seventy-nine, and nine individuals of fifty-one years or above; ten examples of the typhoidal clinical type, an incidence of 27 per cent; fourteen patients with tular-

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emic pneumonia, a frequency of 37.8 per cent, including two with bilateral pneumonia and three with accompanying large pleural effusions. Thus the group was composed of infections of considerably greater average severity than would have been encountered by a random selection. The time of onset of therapy ranged from the second to the one hundred twenty-third days of disease, with the average on the twenty-second day. The usual mode of administration was by intramuscular injection every three hours, occasionally every four hours. A few dangerously ill patients received part of the total amount by continuous intravenous or subcutaneous drips. The periods of administration varied from two to seventeen days, and the total dosage per patient varied from 0.64 to 29.5 Gm.

All published reports[4–15] as well as all private communications received to date, were in agreement that streptomycin modified favorably the course of the disease, usually promptly and often dramatically. The only apparent exceptions were three patients who were treated during the eleventh, seventh and third months of disease.[13] Otherwise the observed objective evidences of improvement were lowered temperature, reduction in diameters of buboes and restoration of mental clarity, usually preceded or accompanied by equally prominent subjective changes, notably relief from headache, sense of prostration, mental depression, arthralgias and myalgias, and lessened pain in primary lesions and in buboes. If pneumonia was present, the additional diminution or disappearance of cough and the reductions in pulse and respiratory rates created a dramatic turn of events. Regardless of the stage of disease at which therapy was instituted the temperature usually fell to normal within seventy-two hours, a highly significant change for the eighteen patients who were given treatment before the fifteenth day of disease, and especially so for the fourteen patients who had tularemic pneumonia. In one case the distressing sequel of serial suppuration of lymphadenopathies was promptly halted.[6] Early treatment did not prevent all suppurative lymphadenitis though it did reduce the frequency to a new low level. Primary lesions that were in the non-ulcerated papular stage at the onset of therapy usually healed without ulceration, and in about one-third to one-half of the usual healing time.

The average results of therapy are shown in Table 1, in comparison with means obtained from untreated patients and from a group that was treated with hyperimmune serum, the latter probably representing the best results obtainable with serum therapy.[7] The extraordinary therapeutic effectiveness of streptomycin is not adequately reflected by the figures presented. This is apparently due to the inclusion in this small series of three patients who were not treated until the seventy-ninth, one hundred third, and one hundred twenty-third days of disease, respectively. Nevertheless a duration of disease of less than two months, and a therapy-to-recovery interval of considerably less than forty-six days are new low constants for tularemia, exceptionably remarkable in view of the late average time of onset of therapy, the twenty-second day of disease. Averages that were more in harmony with the usual clinical experience were obtained by arbitrarily excluding from computations the data from the three late treated patients. These figures, shown within parentheses, are more representative of the results of treatment during the severe acute phase of the disease, and probably foreshadow more accurately the results to be secured eventually by proper analysis of a suitably large series.

Five patients were desperately ill when therapy was initiated on the third, thirteenth, twenty-fourth, twentieth, and fifth

TABLE I

COMPARISON OF MEANS FROM THE CONTROL AND HYPERIMMUNE SERUM TREATED GROUPS WITH AVERAGES FOR THE STREPTOMYCIN TREATED GROUP

| | Untreated N = 542 | Hyperimmune Serum N = 54 | Streptomycin | |
|---|---|---|---|---|
| | | | N = 36 | (N = 33) |
| Duration of: | | | | |
| Disease, months | 3.78 | 2.15 | 1.85 | (1.50) |
| Disability, months | 3.12 | 1.87 | 1.91 | (1.59) |
| Adenopathy, months | 3.50 | 1.78 | 2.03 | (1.73) |
| Fever, days | 30.6 | 28.9 | 29.7 | (23.7) |
| Bed days | 46.8 | 23.3 | 27.5 | (23.3) |
| Primary lesions, days | 40.6 | 30.9 | 27.6 | (27.7) |
| Day of disease therapy was begun | ..... | 17 | 22 | (14) |
| Suppurative adenitis, per cent | 56 | 26.5 | 20 | |
| Mortality, per cent | 6 | 3.3 | 2.7 | |
| Therapy-to-recovery interval, days | ..... | 46 | 38 | (37) |

days of disease, respectively. All exhibited the typhoid state, and two had non-remittent fever at high levels, a symptom combination which in the past has usually been followed by death within seven days. Transitions from the highly febrile, incontinent, stuporous state to one of cheerful competence with sustained progressive improvement were effected within seventy-two hours by treatment of the first four patients. The fifth, a woman of fifty-five who had had signs of pneumonia by the second day of disease, and who had been delirious since the third day, was admitted late on the fourth day and died early in the sixth day despite treatment at the rate of 0.15 Gm. every three hours during the previous fifteen hours.

The duration of pulmonic exudates was measured in ten patients by means of serial chest films. The approximate times of appearance and disappearance of exudates are tabulated in Table II against the day of disease upon which therapy was initiated. Although sufficient accurate data are not available for comparison it is generally known that tularemic pneumonias resolve slowly and that exudates commonly persist for two months and not infrequently throughout the third month of disease. Streptomycin therapy apparently effected a considerable reduction in the resolution time and, on the average, the less the interval between detection of pneumonia and institution of therapy the shorter was the period of repair.

TABLE II

THE DURATION OF PULMONARY EXUDATES IN TEN PATIENTS WHO WERE TREATED WITH STREPTOMYCIN

| Approximate Day of Disease Pneumonia Appeared | Day of Disease Therapy Instituted | Approximate Day of Disease Exudate Disappeared |
|---|---|---|
| 8 | 8 | 28 |
| 7 | 11 | 21 |
| 4 | 11 | 62 |
| 6 | 13 | 31 |
| 1 | 17 | 29 |
| 4 | 18 | 41 |
| 17 | 20 | 38 |
| 10 | 22 | 51 |
| 4 | 24 | 97+ |
| 13 | 79 | 144+ |

Although there is unanimous agreement so far that streptomycin therapy is highly effective in acute tularemia there is obvi-

ously no widespread appreciation of just how effective it really is, nor any agreement about dosage requirements. Perhaps the total experience is too small to expect it. Two dosage plans are discernible in published reports. In one the dosage varies from 1 to 3 Gm. per day for from seven to ten or twelve days, and occasionally longer. Although this "playing safe" policy makes the patient and the physician feel vastly better within a day or two it contributes nothing else beyond a reaffirmation that the antibiotic is effective in this disease. The other shows early attempts to determine the minimal and safest, most efficient dosage range and, through its rewarding, increased insight into disease processes, to lay the groundwork for skilful and economic management. It may not be without significance that those who are most familiar with the disease are using the smaller dosages.

Peterson and Parker[9] secured a brilliant result in a pneumonic patient with temperature peaks reaching 104.2°F. or more daily, using a total of 1.9 Gm. In fact, the dramatic change within twenty-four hours to the afebrile and asymptomatic state was effected by the administration of 0.9 Gm. at the rate of 0.05 Gm. every three hours, for two and one-fourth days, beginning on the eleventh day of disease. The additional 1 Gm. was administered at the same rate, starting three days after cessation of the first amount. Their considered judgment in this case was, "It is doubtful whether the latter series was necessary. The patient had been afebrile for 3 days when the second course was started; he was showing steady improvement, and the subsequent illness did not indicate that the additional streptomycin had been beneficial."

Abel[5] reported an equally satisfactory response in a man with the ulceroglandular type without pneumonia but with large buboes. Two Gm. of streptomycin were administered at a rate of 0.166 Gm. every four hours for two days, starting on the eighth day of disease. He commented, "Inasmuch as the clinical use of streptomycin in tularemia is scant, the yardstick of dosage has not been established. On this basis, only two million units were administered to this patient and the results were just as good as in the previous patient who received 7 million units."

The first seven patients reported by Foshay and Pasternack[4] showed equally satisfactory clinical responses following administration of a usual total dose of 1.2 Gm., with a maximal of 1.76 Gm. One was in the desperately ill classification and another had tularemic peritonitis with the abdominal cavity distended with infected fluid. One experienced a late, recurrent lymphadenitis with rapid necrosis and formation of a subpectoral abscess. A later attempt[7] to approximate a minimal, safely effective dosage, made in another desperately ill patient with bilateral tularemic pneumonia, showed that even an infection of maximal severity was controllable by streptomycin administration at a rate of 0.5 Gm. per day, and that treatment for two or three days at this rate might be expected to be a reasonable maximal requirement. Further evidence to support this probability can be found in the report and in the administration chart of the patient treated by Cohen and Lasser,[8] another desperately ill patient in whom the dramatic turn of events was accomplished by the administration of 0.5 Gm. per day. It is not clear that the subsequently doubled rate was necessary or beneficial. After the dramatic fall in temperature and restoration to consciousness and to a state of progressive improvement each of these latter patients showed irregular, low to moderate fever during the period of earliest favorable changes in the pulmonic exudates. The chart referred to indicates that the period of fever coincided with

specific *in vivo* agglutinin absorption, and that it was, therefore, a consequence of effective therapy and not an indication for more treatment, as they correctly judged.

Untoward reactions have been few. Two patients who were receiving 0.1 Gm. every three hours experienced dermal rashes, one with an accompanying sharp rise in temperature.[13] An unreported patient had a dermal rash, accompanied by a sharp rise in temperature and muscular cramps in the calves, on the eighth day of administration at a rate of 0.15 Gm. every three hours for a total of 9.3 Gm. Subsequent observation at six weeks after discharge from hospital disclosed persisting vertigo and tinnitus. Although many patients showed a small rise in temperature within eight hours of institution of therapy the associated brief intensification of disease symptoms, in the few cases in which it was detectable at all, was negligible and trifling. The only patient to experience the analogue of the Herxheimer reaction was the previously reported one with the infected, massive peritoneal exudate.[4]

## COMMENT

An important practical result of the healing without ulceration of papular primary lesions was that it prevented secondary pyogenic infection of ulcers and, in consequence, greatly reduced the frequency of suppuration of buboes. If a few physicians and patients could have been dissuaded from incising or needling early, unbroken, primary papules it is not unlikely that the incidence of suppurative adenitis in this series would have been lowered still further. It is apparently not widely appreciated that these secondary infections, usually by hemolytic staphylococcus aureus, and especially if the lesions become dry and seal over, appreciably increase the frequency of suppurative adenitis. Indeed, adequate local and, if need be, appropriate systemic therapy to control existing secondary pyogenic infections of ulcers and buboes would contribute materially to lower the bubo suppuration rate. Not all re-enlargements of buboes are due to secondary infection but should a typically effective streptomycin response be followed by recurrence of low to moderate fever, with gradual re-enlargement and increasing tenderness of previously shrunken buboes, it might be remembered that the likelihood of secondary infection is considerably greater, based on experience to date, than a reactivation of the tularemic process. This held true throughout many years of observation of the effects of serum therapy, and it is already becoming evident following streptomycin therapy.

The three patients in the second group reported by Howe, Coriell and associates[13] stand out in marked contrast to all others since therapy administered at the rate of 0.1 Gm. every three hours for from three to seven days failed to induce appreciable immediate favorable changes, and played at most a doubtful part in the recoveries that eventually followed at two, four and three months, respectively, after cessation of therapy. These patients had weathered fairly mild acute phases of the disease and, at the time of treatment, were suffering frequent intermittent attacks of low to moderate fever associated with sense of prostration, great fatiguability and, in one case, generalized enlargements of lymph nodes. The association of transitory *in vivo* specific agglutinin absorptions with recurrent exacerbations of symptoms characteristic of tularemia makes any other cause for the chronic illnesses highly improbable. Considerations of the mild character of the acute phases, the previous prophylactic vaccinations, or the late stages of disease at which therapy was initiated have suggested no plausible reasons for the state of refractoriness to therapy. One might suspect that

the locations, presumably intracellular, in which the surviving bacteria were held in inadequate or impermanent bacteriostatic equilibrium were impermeable to streptomycin at the prevailing concentrations. In any event it seems more probable that the fundamental abnormality in such cases is a defect in the individual's defense apparatus rather than in the activity of the antibiotic. Similar examples have been observed among unvaccinated laboratory personnel.[16] The clinical courses and the responses to streptomycin therapy of these uncommonly seen examples of chronic tularemia resemble those of subacute or early chronic brucellosis so very closely that it suggests some common causative feature in the respective host-parasite relationships.

Although it seems that most physicians are using far larger amounts of streptomycin than are really necessary for their patients, it is in relation to this very matter of suppurative adenitis that the effect of total quantities larger than 2 or 3 Gm. per patient might be studied much more, particularly in patients with buboes with diameters of 5 cm. or more at the time treatment is initiated. Buboes of this size seldom escaped eventual suppuration in the pre-streptomycin days. Several patients in this series had liquefaction necroses after total dosages of 1 to 3 Gm. On the other hand another, who had no nodes palpable when therapy was started on the fifteenth day of disease, received 1 Gm. per day for seven days, and then developed rapid re-enlargement and liquefaction of an axillary node which required drainage on the tenth day after cessation of therapy. Others who received 6, 8 or even 20 Gm. of streptomycin still have large nodes, some tender and fluctuating in size, whose ultimate outcome cannot be predicted. Since buboes that may have disappeared entirely with or without treatment are known to re-enlarge and to progress rapidly to liquefaction up to six or twelve or even to thirty months after recovery there can be no assurance of success but it seems justifiable to try larger dosage to see if this will further reduce the incidence of suppurations. The crux of the matter seems to be the difficulty in distinguishing between the results of persisting or of mixed infection and the consequences of irreversible tissue damage that may have been inflicted prior to the onset of therapy.

The patient with the typhoidal clinical type, often with tularemic pneumonia but clearly not in the desperately ill category, is the one who is presently receiving the largest therapeutic doses. Although it may seem contrary to expectations based upon experience with other infections it is precisely this type of tularemic infection which responds dramatically to the smaller total dosages of 2 or 3 Gm. administered over a four to six-day period. The importance of treating infections with high initial concentrations of bacteriostatic or bactericidal agents is not minimized; the sensitivity of *Bacterium tularense* to streptomycin is simply so high that adequate initial blood concentrations are easily achieved by the above recommended dosage which, furthermore, is much less apt to induce hypersensitivity or other toxic or undesirable drug reactions.

The problem of the fulminant case, the one person out of approximately each thousand who reacts to invasion with no more effective resistance than does the rabbit, and who similarly dies between the fifth and tenth days of disease, is one of early diagnosis. The amazing effectiveness of streptomycin in totally non-resistant laboratory animals justifies the expectation that these deaths could be prevented if treatment could be given early enough.

## SUMMARY

There is uniform agreement that streptomycin is an extremely effective thera-

peutic agent in tularemia. Although the experience is too small to permit formulation of an optimal dosage, no evidence has yet appeared that either (1) 0.5 Gm. per day for two days followed by 0.25 Gm. per day for four days or (2) 0.5 Gm. per day for six days is not adequate dosage for the case of usual severity, with or without tularemic pneumonia.

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# Treatment of Urinary Tract Infections with Streptomycin*

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THE earliest reports indicated that streptomycin effectively inhibited the growth of most of the gram-negative bacteria responsible for infection of the urinary tract.[1,2,3,4] Clinical studies have indicated the importance of anatomical conditions prevailing in the genitourinary tract and the bacterial flora producing infection as factors influencing the results obtained from treatment with streptomycin.[5,6,7,8,9] The purpose of this report is to review briefly the basic pharmacological and bacteriological data of direct importance in the treatment of urinary tract infections and to summarize the experience at the Massachusetts Memorial Hospitals as illustrative of the present state of our knowledge concerning the use of this chemotherapeutic agent in the management of these infections.

## PHARMACOLOGY

Streptomycin administered intramuscularly produces maximum blood levels within one to two hours after injection and appears rapidly in the urine during the first hour after injection. After a single dose of streptomycin the urinary excretion of the drug is greatest during the four hours following injection corresponding to the period of highest blood levels and continues over a twenty-four to forty-eight hour period.[10,11,12] The rate of renal excretion of streptomycin is thus considerably slower than that of penicillin. One hour after injection 60 per cent of a given dose of penicillin can be recovered from the urine and excretion is almost complete within four hours whereas 20 to 30 per cent of a single dose of streptomycin is excreted later than four hours after administration.

The concentration of streptomycin in the urine is related to the dose of the drug, urine volume and renal function. Considerable variation exists in the total amount and in the concentration of streptomycin excreted in the urine. Sixty to 80 per cent of the dose administered usually appears in the urine and on dosage schedules of 2 to 4 Gm. per day concentrations of 25 to 5,000 micrograms per cc. of urine may be obtained. In our cases in which it has been feasible to limit the daily fluid intake to 2,500 cc. and with a daily dose of 1 Gm. of streptomycin a minimum urine level of 100 micrograms per cc. has been present almost uniformly. Two Gm. of streptomycin daily usually has insured a urine level of 250 micrograms per cc. The concomitant use of oral alkali with streptomycin has not produced any significant effect on the urinary excretion of the drug. Several investigators have observed patients with advanced renal disease who manifest decreased renal excretion of streptomycin with low urine levels and markedly increased serum levels.[8,11] We have not observed this phenomenon, but in occasional instances it may be of therapeutic importance by preventing urine levels adequate for bacter-

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icidal action. In connection with the treatment of renal and urinary tract infections the work of Adcock and Hettig is of interest in which postmortem assays were performed on the organs of two patients receiving streptomycin and the amount of the drug in renal tissue was found to be approximately twice that present in the serum whereas considerably smaller amounts were present in the lung and heart muscle.[13]

## BACTERIOLOGY

The bacteria which occur most commonly in urinary tract infections are gram-negative bacilli of which Escherichia coli and Aerobacter aerogenes are most frequently isolated. Gram-positive cocci may also be present, and of the streptococci the nonhemolytic enterococcus group and alpha hemolytic streptococci are more common then beta hemolytic types. The relative frequency of various groups of bacteria in the series reported by Braasch[14] and by DeBakey and Pulaski[15] is cited in Table 1 for comparison with our own cases. Urinary tract infections may occur with a single organism or a mixed infection with several types of bacteria may be present. The frequency with which groups of organisms different from those originally present appear during treatment suggests that mixed infections may be more frequent than previously supposed and that infections which are apparently caused by a single group of bacteria may in some instances represent the predominance of one group which when suppressed allows other types to appear in numbers capable of detection. This phenomenon was observed in 31 per cent of our cases. Gram-positive cocci insusceptible to streptomycin occasionally appear in the urine following suppression of gram-negative bacilli and the appearance of gram-positive cocci in the sputum, nose and throat in some instances followed by fulminant infections must be remembered as a possible complication of streptomycin therapy.[16]

TABLE 1
FREQUENCY OF OCCURRENCE OF BACTERIA IN URINARY TRACT INFECTIONS

| Organism | Braasch[14] | DeBakey Pulaski[15] | Mass. Mem. Hosp. Series |
|---|---|---|---|
| Total cases | 200 | 680 | 75 |
| E. coli | 84 | 132 | 51 |
| A. aerogenes | 26 | 170 | 17 |
| Staphylococci | 28 | 58 | 2 |
| S. fecalis | 8 | 83 | 12 |
| Proteus sp | 6 | 115 | 18 |
| P. aeruginosa | ... | 70 | 12 |
| B. mucosus | ... | 32 | 8 |
| H. influenzae | ... | ... | 1 |
| Mixed infections | 17 | ... | 33 |

Most of the organisms encountered in urinary tract infections are susceptible *in vitro* to the concentration of streptomycin obtainable in the urine although cultures which are naturally resistant are encountered. These are relatively infrequent except for Pseudomonas aeruginosa and Streptococcus fecalis. Published reports and our own experience indicates that about 75 per cent of the cultures of E. coli, A. aerogenes and Proteus sp. are sensitive to a concentration of streptomycin of twenty micrograms or less per cubic centimeter. All of the fourteen cultures of Proteus sp. we have tested have been sensitive to less than 20 micrograms of streptomycin per cc. A concentration of streptomycin of over 100 micrograms per cc. was required to inhibit two of nine cultures of Pseudomonas aeruginosa and six of twelve cultures of Streptococcus fecalis. Although E. coli, A. aerogenes and Proteus sp. are usually quite sensitive to streptomycin *in vitro*, Helmholz found that under the experimental conditions he employed urine containing less than 66 micrograms per cc. produced no interference with growth and that a concentration of at least 100 micrograms per cc. was necessary before

bactericidal effect on Pseudomonas aeruginosa and Streptococcus fecalis was observed.[17] Furthermore, the number of bacteria commonly present in urinary tract infections exceeds considerably the number employed under the experimental conditions of the *in vitro* sensitivity test and a large margin of safety is probably important in determining the urine level of streptomycin desired on the basis of the sensitivity of the organisms which are present. The decreased antibacterial effect *in vitro* of streptomycin when the pH of the culture medium is less than 7.0 is well known. Wolinsky and Steenken[30] noted a progressive decrease in antibacterial effect as the pH of the culture medium was decreased from 7.7 to 5.2 with the most marked diminution occurring between pH 6.6 and 5.9. No destruction of streptomycin occurs nor has any change been observed in its antibacterial activity in the presence of purulent or non-purulent exudates, serous transudates or normal tissue juices. The presence of procaine likewise produces no neutralization of antibacterial activity.

The ease with which bacteria develop resistance to the antibacterial action of streptomycin has been well demonstrated.[18,19,20] This phenomenon represents the primary factor limiting the therapeutic efficiency of this drug. The degree to which streptomycin resistance can develop is of a high order of magnitude. By successive transfer into media containing increasing concentrations of streptomyoin cultures can be obtained of all of the gram-negative bacilli occurring in urinary tract infections which grow readily in the presence of streptomycin in concentrations of 25,000 to 50,000 micrograms per cc. This represents absolute resistance for therapeutic purposes. Bacteria recovered routinely from patients with urinary tract infections in which bacteriological cure has not occurred frequently possess this same order of resistance.[21] These organisms do not differ significantly morphologically or in the biochemical reactions they produce from the original cultures from which they were derived although a change in pigment production and a reduction in rate of carbohydrate fermentation by staphylococci which have become streptomycin resistant *in vitro* has been noted.[20] No relationship has been observed between the sensitivity of bacteria to streptomycin and their response to other chemotherapeutic agents. Cultures which have become resistant either *in vitro* or *in vivo* to high concentrations of streptomycin manifest the same degree of sensitivity to penicillin and to sulfonamides as they did before exposure to streptomycin.[20,22]

The rate at which streptomycin resistance develops may be quite rapid particularly when compared with the rate of the development of penicillin resistance. Employing the usual *in vitro* technic Knop[23] studied the development of resistance to streptomycin of cultures of E. coli, A. aerogenes and Proteus sp. which were sensitive to a concentration of 6 micrograms per cc. Seven transfers were sufficient to produce cultures resistant to 1,000 micrograms per cc. in some instances and all the cultures became resistant to this concentration of streptomycin in twelve to twenty-four transfers. The use of nutrient broth or urine as a culture medium did not produce any significant difference in these results except when Proteus sp. was grown in urine containing streptomycin. Bactericidal action occurred so readily under these circumstances that the development of resistant bacteria was difficult. A possible explanation for this difficulty is the ability of this organism to decompose the urea present in urine with formation of ammonia and production of an alkaline medium in which the activity of streptomycin is greatly enhanced. Cultures of Pseudomonas aeruginosa and Streptococcus fecalis developed streptomycin resistance more readily than the other bacteria tested.

## CLINICAL MATERIAL

A number of reports have appeared concerning the treatment of urinary tract infections with streptomycin.[5,9,15,21,24,26] Seventy-five cases of urinary tract infections have been treated at the Massachusetts Memorial Hospitals.* The published reports and our own cases may be divided into several clinical groups in which the effectiveness of streptomycin can be evaluated separately.

*Acute Pyelonephritis.* Eight patients with acute urinary tract infection with marked constitutional symptoms and signs have been treated. Seven of these patients showed dramatic clinical improvement with rapid decrease of fever, costovertebral angle tenderness, leukocytosis, and pyuria and improvement in renal function. In several instances this improvement was of value in preparation of the patient for surgery. With clinical improvement bacilluria has usually been temporarily reduced on the basis of quantitative measurements by the plate count method but in only one case did sterilization of the urine occur. Pyuria was decreased in six cases but disappeared in none. Control of bacteremia which frequently accompanies acute pyelonephritis may be of importance in producing a good clinical response.

*Pyelonephritis of Pregnancy.* Nine cases of pyelonephritis of pregnancy have been treated all of which have manifested symptoms and signs consistent with moderate or severe acute pyelonephritis rather than merely pyuria and bacilluria. Inasmuch as symptoms and fever commonly subside on a regimen of bed rest and administration of large volumes of fluid, evaluation of the rôle played by streptomycin in these cases is difficult. Six patients manifested an excellent clinical response with decreased pyuria and bacilluria and three of these showed sterilization of the urine. Pyuria almost disappeared in the three patients whose urine became sterile. Two of the three bacteriological cures relapsed within one month following discharge from the hospital but in both cases the bacteria isolated were sensitive to concentrations of streptomycin less than 32 micrograms per cc.

*Chronic Pyelonephritis.* Eighteen patients with urinary tract infections have been treated in which some anatomical obstruction to the free flow of urine has been present. Sterilization of the urine occurred in only three (17 per cent) of these patients. Fourteen cases of urinary tract infections have been treated in which no obstructive element could be found with urinary sterilization in eleven (79 per cent) of these patients. Pyuria responded more irregularly than bacilluria. Whereas bacilluria was frequently reduced temporarily in those cases in which bacteriological cure was not attained, pyuria frequently continued undiminished and in only eight of the twenty-nine instances of urinary sterilization in our entire series did pyuria cease. The response of mild urinary tract symptoms and low grade fever associated with chronic pyelonephritis was also quite irregular.

Calculi were present in eleven of our cases accompanied by Proteus sp. in seven instances. Clinical improvement was noted in nine patients who were experiencing acute exacerbations of chronic pyelonephritis but bacteriuria ceased in only three cases. Two of these underwent nephrectomy rendering it impossible to attribute bacteriological cure to streptomycin and the third patient developed recurrent bacteriuria four days after cessation of streptomycin therapy. It is worthy of note, however, that

* The urological care of these cases was the responsibility of Drs. S. N. Vose and D. L. Anderson without whose cooperation these studies would not have been possible.

Streptomycin was provided by The National Research Council from supplies assigned for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents, Dr. Chester S. Keefer, Chairman.

Proteus sp. was eradicated from the urine and the urine became acid in all cases although other gram-negative rods persisted.

The importance of anatomical complications producing urinary stasis has been noted by others. Pulaski[8] reported four cases of calculi with two bacteriological cures both of which had simultaneous surgical removal of the calculi. Of twenty-six patients with calculi reported by DeBakey and Pulaski[15] only four showed improvement with no data being given concerning urinary sterilization. Harrell et al.[26] grouped cases as complicated and uncomplicated and noted good results in twenty-five of twenty-eight cases in the latter group as contrasted with four of twenty-four patients in the former group.

*Preoperative and Postoperative Use of Streptomycin in Relation to Genitourinary Surgery.* Streptomycin has been of value in controlling severe constitutional manifestations of acute infection of the urinary tract prior to surgery. The clinical response to streptomycin therapy of acute pyelonephritis occasionally with bacteremia has permitted extensive genitourinary surgery under much more favorable conditions than existed prior to chemotherapy. In situations in which sulfonamides are contraindicated, as in the presence of ureteral obstruction by stone, streptomycin is the chemotherapeutic agent of choice. When the circumstances for bacteriological cure are unfavorable due to the presence of obstruction, calculi, undrained abscesses or catheters, the development of bacteria resistant to streptomycin may preclude the usefulness of the drug during the postoperative period. When the main source of infection is to be removed as in nephrectomy this difficulty may to some extent be obviated. The clinical response to streptomycin of patients with abscesses associated with the genitourinary tract has been poor in the cases reported and in the three cases of perinephric infection treated by us clinical improvement was obtained in only one patient who had undergone surgical drainage prior to institution of streptomycin. The use of streptomycin in the presence of localized accumulations of exudate affords bacteria an ideal opportunity for development of resistance by exposing them to concentrations of a chemotherapeutic agent inadequate to insure bactericidal action.

The use of streptomycin preoperatively or postoperatively in patients in whom urological indications demand catheter drainage has been uniformly disappointing. The indwelling catheter, suprapubic cystostomy or nephrostomy tube acting as a foreign body is accompanied by the development or introduction of bacteria resistant to streptomycin. Four patients who had sterile urine and who were to have urological procedures necessitating an indwelling catheter preoperatively were placed on a daily dose of streptomycin of 4 Gm. prior to insertion of the catheter. Within seven days urine culture of each patient revealed gram-negative bacilli which were resistant to a concentration of streptomycin of 5,000 micrograms per cc. In only a single case in our entire series was sterilization of the urine accomplished in the presence of an indwelling catheter. The use of streptomycin under these conditions should be limited to those patients manifesting severe, uncontrolled acute upper urinary tract disease or bacteremia associated with urinary tract disease.

Lower urinary tract infection with persistent pyuria is one of the troublesome and frequent complications of transurethral prostatic resection. In an effort to shorten the period during which pyuria and bacilluria were present ten patients were given streptomycin following transurethral resection of the prostate, five being given a daily dose of 1 Gm. and five a daily dose of ½ Gm. Decreased pyuria or bacilluria was not observed during or after streptomycin

therapy. The bacteria present prior to treatment in all cases were sensitive to a concentration of streptomycin less than 64 micrograms per cc. and those isolated after completion of treatment were resistant to concentrations of streptomycin over 10,000 micrograms per cc.

*Urinary Tract Infections Associated with Paraplegia.* Petroff and Lucas[7] reported thirty-five cases of urinary tract infection associated with paraplegia treated with comparatively small doses of streptomycin. In thirteen patients who had automatic bladders and were voiding without use of catheters sterilization of the urine occurred in nine cases but all became reinfected within four days. The treatment of twenty-two cases with indwelling catheters present resulted in urinary sterilization of ten patients for a period of one to two days but bacteria were again recovered from all patients within four days. Pulaski[8] reported bacteriological cure in three of eight paraplegics treated with a daily dose of streptomycin of 2.4 Gm. The patients in whom urinary sterilization was observed did not have suprapubic fistulas or residual urine. The largest series of 221 cases has been reported by DeBakey and Pulaski.[15] In patients in whom calculi were not present improvement was noted in 35 per cent of those treated. When calculi were present improvement occurred in only 11 per cent of patients treated and when undrained abscesses or cellulitis were present good results were observed in only 7 per cent of the patients treated.

*Acute Epididymitis.* We have treated two patients with acute epididymitis. One case occurred following dilatation of a urethral stricture and the other followed transurethral prostatic resection. Gram-negative bacilli persisted in the urine during streptomycin therapy but dramatic relief of pain with rapid reduction in scrotal swelling and tenderness occurred twenty-four hours after institution of chemotherapy. Six other cases of epididymitis have been reported with similar good clinical results in three instances and failure in three patients in which surgical treatment was necessary.[5,26,31]

*Urethritis.* Streptomycin has not been used extensively in urethritis. Neisseria gonorrhoeae is quite susceptible to streptomycin *in vitro*.[19,27] Five cases of gonococcal urethritis have been reported with cure in all cases.[15]

## BACTERIOLOGICAL FEATURES OF CLINICAL MATERIAL

Forty-two single infections and thirty-three mixed infections were present in our series. Infections with a single type of organism responded as well clinically as did those with mixed bacterial flora in the urine. Definite clinical improvement was observed in 64 per cent of the patients with each type of infection. However, sterilization of the

TABLE II
BACTERIOLOGY AND RESULTS OF TREATMENT OF URINARY TRACT INFECTIONS

| Type of Infection | No. of Cases | Good Clinical Result | Poor or Indefinite Response | Bacteriuria after Treatment | |
|---|---|---|---|---|---|
| | | | | Present | Absent |
| Single organism.. | 42 | 27 | 15 | 20 | 22 |
| E. coli..... | 24 | 15 | 9 | 13 | 11 |
| A. aerogenes... | 4 | 1 | 3 | 4 | 0 |
| Proteus sp..... | 6 | 5 | 1 | 0 | 6 |
| P. aeruginosa.. | 4 | 3 | 1 | 2 | 2 |
| B. mucosus.... | 1 | 1 | .. | 0 | 1 |
| S. fecalis..... | 2 | 1 | 1 | 0 | 2 |
| H. influenzae.. | 1 | 1 | .. | 1 | .. |
| Mixed infections. | 33 | 21 | 12 | 26 | 7 |
| E. coli..... | 27 | 15 | 12 | 20 | 7 |
| A. aerogenes... | 14 | 9 | 5 | 8 | 6 |
| Proteus sp..... | 12 | 7 | 5 | 2 | 10 |
| P. aeruginosa.. | 9 | 6 | 3 | 2 | 7 |
| B. mucosus.... | 7 | 3 | 4 | 3 | 4 |
| S. fecalis..... | 10 | 7 | 3 | 3 | 7 |
| Total..... | 75 | 48 | 27 | 46 | 29 |

urine occurred in 52 per cent of the patients with a single type of infecting organism and in 21 per cent of those with mixed bacteriological flora. The overall recovery rate was 39 per cent. These results are in accord with those obtained in the 409 cases reported by Keefer et al.[32] The frequency with which each specific organism was eradicated from the urine is given in Table II. Infections with E. coli, A. aerogenes, P. aeruginosa and S. fecalis appeared to respond about equally well to streptomycin. Proteus sp. was present in eighteen cases of urinary tract infection. This organism disappeared from the urine in sixteen patients (89 per cent) which is significantly higher than for the other groups of bacteria. This might indicate that Proteus sp. responds at least temporarily more favorably than other bacteria but the alkaline reaction of the urine in infections in which this organism is present may explain the apparently increased susceptibility of Proteus sp. infections. Sterilization of the urine may occur quite rapidly following administration of streptomycin. Negative urine cultures have been obtained twelve hours after institution of therapy and all of our nineteen bacteriologic cures showed sterile urine at the end of forty-eight hours of therapy.

TABLE III
STREPTOMYCIN SENSITIVITY OF BACTERIA ISOLATED FROM URINARY TRACT INFECTIONS

| Type of Bacteria | No. of Cultures Isolated | Sensitivity of Cultures Prior to Treatment | | Frequency of Persistence of Bact. Related to Initial Sensitivity | |
|---|---|---|---|---|---|
| | | Less than 64 micrograms per cc. | Over 64 micrograms per cc. | Less than 64 micrograms per cc. | Over 64 micrograms per cc. |
| P. aeruginosa | 9 | 7 | 2 | 1 | 2 |
| S. fecalis | 12 | 6 | 6 | 0 | 3 |
| E. coli | 41 | 41 | 0 | 26 | .. |
| A. aerogenes | 16 | 16 | 0 | 8 | .. |
| Proteus sp | 15 | 15 | 0 | 1 | .. |
| B. mucosus | 8 | 8 | 0 | 3 | .. |

The streptomycin sensitivity of the bacteria present in the urine of the cases treated is presented in Table III. The only naturally resistant bacteria encountered were P. aeruginosa and S. fecalis. The six resistant cultures of S. fecalis required a concentration of streptomycin of 250 micrograms per cc. to inhibit their growth. Naturally resistant strains of both of these organisms are relatively frequent. Within the group of sensitive organisms no correlation was observed between degree of sensitivity and therapeutic success so that the isolation of an extremely sensitive organism afforded no information of prognostic value.

## METHOD OF TREATMENT

The daily dosage of streptomycin employed by us has varied from 1 Gm. to 4 Gm. administered by the intermittent intramuscular method with time intervals of three or six hours between injections. The duration of treatment has been five to seven days in most cases. The average daily dose has been 1.5 Gm. given for an average of 7.9 days. The average total dose has been 11.6 Gm. Alkalinization of the urine with 2 Gm. of sodium bicarbonate or 2 Gm. of sodium citrate every four hours has been employed in conjunction with streptomycin in eleven cases.

In our cases no correlation has been observed between the amount of the daily dose of streptomycin and sterilization of the urine. Bacteriological arrest occurred in 31 per cent, 29 per cent, and 33 per cent respectively of patients given daily doses of 1 Gm., 2 Gm. and 4 Gm. Urinary concentration of streptomycin of 100 micrograms per cc. is desirable, and in our experience, 1 Gm. of streptomycin daily is the

minimum amount which will in most cases insure this concentration.

The strikingly increased antibacterial action of streptomycin *in vitro* at an alkaline pH prompted numerous investigators to suggest alkalinization of the urine in conjunction with streptomycin therapy.[6,9,21,26,27] In sixty-four cases we have treated without the administration of alkali concomitantly with streptomycin bacteriuria ceased in 20 per cent and in eleven cases given alkali during streptomycin therapy bacteriuria disappeared in 73 per cent. (Table IV.)

TABLE IV
COMBINED USE OF STREPTOMYCIN AND ALKALI IN THE TREATMENT OF URINARY TRACT INFECTIONS

| Type of Therapy | Total Cases | Bacteriuria after Therapy | |
|---|---|---|---|
| | | Present | Absent |
| Streptomycin without concomitant alkali therapy | 64 | 51 | 13 |
| Streptomycin with concomitant alkali therapy | 11 | 3 | 8 |

The local use of streptomycin in the urinary tract by irrigation through catheters has not been of value in urinary sterilization in the small number of reported cases.[7,8]

## FACTORS DETERMINING CURE

It is possible to make a preliminary classification concerning the importance to therapeutic success of the various factors which one must consider in the treatment of urinary tract infections. Data are not yet available concerning the permanency of the cures obtained and it has been previously shown that the usual laboratory tests are of little value in prognosis for patients in whom urinary tract infections have been arrested with sulfonamides.[29]

The largest group of therapeutic failures occurs in patients in whom anatomical abnormalities of the genitourinary tract are present which prevent the free flow of urine and allow the accumulation of residual urine. Reduction of the number of bacteria in the urine may occur with streptomycin therapy but the bacterial count returns to its former level either during or immediately after termination of treatment. Foreign bodies in the urinary tract such as calculi, indwelling catheters, suprapubic cystostomy or nephrostomy tubes offer a convenient portal of entry for reinfection and predispose to the development of bacteria resistant to streptomycin. Undrained abscesses represent foci which are inaccessible to chemotherapeutic agents and prevent clinical improvement or bacteriological cure. Wounds with granulating surfaces or fistulas communicating with the urinary tract offer such favorable conditions for bacterial growth that sterilization of the urine cannot be accomplished under such conditions.

The development by bacteria of high resistance to streptomycin is to be regarded as the major factor in therapeutic failure. This phenomenon is observed frequently during the treatment of urinary tract infections but also occurs during the treatment of bacteremia and pneumonia. Bacteremia may arise from an organism which has become streptomycin resistant in the urinary tract. We have treated two of these patients in one of whom the etiologic organism was Pseudomonas aeruginosa and in the other Aerobacter aerogenes. Streptomycin was of no value in controlling the bacteremia in either instance. The method by which streptomycin resistant organisms appear is not completely understood. Resistant bacteria may be derived from sensitive organisms following exposure to streptomycin by a change which occurs in their metabolism or resistant bacteria may be already present in the original culture and grow into predominance following suppression of sensitive organisms. In accordance with the perma-

nence of streptomycin resistance produced by *in vitro* methods is the persistence of resistant organisms in the urinary tract for long periods. Eight patients in whom bacteriuria was present with streptomycin resistant gram-negative bacilli at the termination of streptomycin therapy were re-examined six months after treatment and in all cases resistant bacilli were still present. Other bacteria had appeared in five cases which were sensitive to streptomycin but they had not been present before or during streptomycin therapy and probably represented new invaders. It is of interest, however, that the bacteria recovered at the termination of treatment grew well in the presence of 25,000 to 50,000 units of streptomycin per cc. but those isolated six months later were now sensitive to a concentration of streptomycin of 5,000 units per cc. but resistant to a concentration of 2,500 units per cc.

Mixed infections are more persistent than infections with single organisms. The anatomical lesions associated with mixed infections are frequently more complex and many of the bacteria are resistant to streptomycin. Within the range of bacterial sensitivity to streptomycin which governs the treatment of urinary tract infections variation in sensitivity does not appear to be of importance. Our experience confirms that of others[26] in that bacteria sensitive to a concentration of 2 micrograms per cc. before treatment were as likely to be replaced by highly resistant bacteria of the same type as were organisms with an initial sensitivity of 32 micrograms per cc.

In the presence of bacteria which are within the usual range of sensitivity no additional benefit derives from increasing the dose of streptomycin over that which will insure a urinary concentration of 100 micrograms per cc. In only rare instances was the urine concentration of streptomycin lower than 100 micrograms per cc. when a daily dose of 1 Gm. was employed providing the fluid intake was limited to 2,500 cc. per day. This is a useful method of conserving material and increasing the concentration of streptomycin in the urine. When fluid intake must be maintained at a higher level the dose of streptomycin should be correspondingly increased. When bacteria of known borderline resistance are present or when Pseudomonas aeruginosa or Streptococcus fecalis are cultured from the urine a minimum dosage of 2 Gm. is advisable. Increasing the dose in an effort to eradicate resistant bacteria or organisms which are becoming resistant is a practise without rational basis. The use of maximum dosage is indicated at the time treatment is instituted, and when bacteria resistant to streptomycin are known to be present and continuing clinical improvement does not justify prolongation of streptomycin therapy a different chemotherapeutic agent should be selected promptly inasmuch as the response to other agents is not altered by the appearance of streptomycin resistance. The duration of treatment which is necessary to insure the best long term results is not known. In those cases in which sterilization of the urine occurs the urine culture usually becomes negative within seventy-two hours after initiation of therapy.[21,26] In our own experience persistence of bacteriuria after seventy-two hours of treatment signifies the development of streptomycin resistant organisms. Beneficial clinical results may be apparent upon continuatoin of therapy even though the number of bacteriological cures is not increased.

The concomitant use of alkali and streptomycin to maintain the urine at an alkaline pH at which the activity of streptomycin is considerably enhanced increases the number of bacteriological cures obtained. Sodium bicarbonate, sodium or potassium citrate in doses of 2 Gm. every four hours is usually sufficient to maintain

the urine alkaline. Objections have been made to the use of alkali when Proteus sp. is present in the urine since an alkaline medium increases the rate of growth of this organism and encourages precipitation of calcium phosphate.[8] The use of alkali may not be necessary in pure Proteus sp. urinary tract infections if the urine pH is carefully followed as the urine is usually alkaline when this organism is present. When infection with a mixed bacterial flora in which Proteus sp. is present occurs the urine may become acid following disappearance of Proteus sp. and alkali will then be required to maintain the urine at an alkaline pH. Careful observation should be made for the consequences in cardiac patients of fluid retention following a large intake of sodium.

## SUMMARY

1. After parenteral administration streptomycin appears rapidly in the urine, from which 60 to 80 per cent of the dose administered can be recovered over a period of twenty-four to forty-eight hours after injection. The concentration of streptomycin in the urine is related to the dose administered, volume of urine, and renal function.

2. The bacteria which occur most commonly in urinary tract infections are Escherichia coli, Aerobacter aerogenes, Proteus sp., Pseudomonas aeruginosa and Streptococcus fecalis. About 75 per cent of the cultures of E. coli, A. aerogenes, and Proteus sp. are sensitive to a concentration of streptomycin of 20 micrograms per cc. or less. Cultures of P. aeruginosa and S. fecalis frequently occur which are naturally resistant and require a minimum concentration of 100 micrograms per cc. to inhibit their growth.

3. The marked constitutional symptoms and signs accompanying acute pyelonephritis or acute exacerbations of chronic pyelonephritis usually respond dramatically to streptomycin. Mild urinary tract symptoms and low grade fever respond irregularly to streptomycin therapy. Definite clinical improvement was observed in 64 per cent of our cases.

4. Limitation of fluid intake to 2,500 cc. daily and a dose of streptomycin of 1 Gm. per day will usually insure a urinary concentration of 100 micrograms per cc. which appears to be adequate for the treatment of urinary tract infections providing other factors are favorable for cure. If Pseudomonas aeruginosa or Streptococcus fecalis are present a higher urinary concentration is desirable and a daily dose of 2 Gm. should probably be employed.

5. Bacteriuria is diminished temporarily in almost all patients treated with streptomycin. Urinary sterilization occurred in 39 per cent of our cases, with cases in which only a single group of bacteria was present responding more favorably than those in which a mixed bacterial flora was present. Persistence of bacteria after forty-eight hours of treatment usually signifies the development of streptomycin resistance. Exposure to streptomycin does not alter the response of bacteria to other chemotherapeutic agents.

6. The readiness with which bacteria present in the urinary tract develop resistance to streptomycin is the major cause of failure to achieve urinary sterilization. Bacteremia with bacteria resistant to streptomycin may arise from a focus in the urinary tract. Previous treatment with streptomycin may preclude its successful use at a later time because of the persistence of streptomycin-resistant bacteria in the urinary tract.

7. In the presence of anatomical abnormalities presenting indications for urological treatment streptomycin therapy is disappointing. Poor results are to be expected from streptomycin therapy when the following conditions exist in the urinary tract: (1) obstruction which prevents the

free flow of urine and permits accumulation of residual urine, (2) foreign bodies such as calculi or indwelling catheters, (3) wounds with granulating surfaces, and (4) undrained abscesses. Good results are to be anticipated under these conditions only if urological treatment is undertaken prior to or in conjunction with streptomycin therapy.

8. Alkalinization of the urine concomitantly with streptomycin therapy increases significantly the incidence of sterilization of the urine with streptomycin treatment.

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# Streptomycin Therapy in Undulant Fever

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THE first case of "Malta Fever" was recognized in Iowa in 1926. During the following year, forty-three cases were reported to the Iowa Department of Preventable Diseases. Since 1927, the yearly reviews on undulant fever indicate that Iowa has had the largest number of reported cases in the United States. For the first eleven months of 1946, over 500 cases were reported in Iowa and there was only one death. This patient died with congestive heart failure. Blood cultures were positive for Br. suis previous to death and the autopsy revealed vegetative endocarditis of the aortic valves. The organisms were isolated in pure culture from the aortic vegetations and the disease was then experimentally reproduced in the guinea pig.

The early cases of undulant fever were diagnosed only by the agglutination test; but later we learned that the agglutination test was not infallible and today we regard a positive agglutination test as only presumptive evidence of active disease. We all know that there are a number of factors that give cross-agglutinations and false positive agglutinins, and thus lead to positive agglutinations for undulant fever in patients that are ill from other diseases. The skin test has never been used as a diagnostic aid in any of my cases. Since 1939, the brucella organism has been isolated from the blood of my undulant fever patients. All patients were seen early in the course of their illness, and this undoubtedly explains in part the large number of positive blood cultures. The diagnosis of undulant fever was not accepted in any of my cases unless the blood culture was positive. I have observed two patients with positive blood cultures in whom the clinical history was suggestive (agglutination positive in a high titre), and yet the patients never lost a day from their work. These patients were observed over a two-year period and they did not have any recurrence of symptoms suggestive of undulant fever. In a few instances a positive blood culture may be obtained in patients not acutely ill. The patient's history, physical findings, exposure, clinical course and complications must be considered along with the laboratory tests before a positive diagnosis of undulant fever can be established.

My first patient was treated in October, 1927, and received enesol (bismuth-mercury preparation) intramuscularly. From 1929 to 1935, many patients were treated with vaccines and brucelline (both in the recommended 0.55 cc. and 1.0 cc. intramuscular injections); and in 1944, intradermal brucelline in 0.1 to 0.22 was used. The heavy brucelline dose was discontinued because of the frequent and pronounced reactions. Very little reaction developed from the intradermal injection. This method was used in four patients but the results were not impressive. Convalescent serum was tried in two patients who were treated in 1939 and in 1940. Both patients had a Brucella suis organism in their blood streams. Convalescent serum was obtained from patients with undulant fever who had recently recovered from the disease. Each of the donors had had the suis variety of the brucella. The clinical response was satisfactory but it was impossible to secure an adequate serum bank to give this therapeutic agent a con-

vincing test in a large number of patients. Sulfonamide treatments were started in 1939 but the therapeutic results were unsatisfactory. There were many recurrences even though the blood concentration of the drug was maintained at a high level for a period of seven to ten days. In 1944, based upon Tsun Tung's[1] experimental work, patients with undulant fever were treated with a combination of sulfathiazole and penicillin. From 1944 to 1946, twenty-eight of my patients were treated by this combined therapy and twenty-four were improved. There were four failures. Any patient developing a recurrence, even though the relapse was from one to three weeks' duration only, was automatically classified as unsuccessful. The twenty-four patients previously mentioned were successfully treated as far as acute symptoms were concerned; however, the blood culture remained positive at the completion of the treatment and continued positive for one and two months during the convalescent stage. All of my patients had an extended (six to twelve months) period of convalescence. Vitamins, tonics, liver, iron and blood transfusions had no effect in reducing this period in any of these patients.

For a period of nineteen years, then, I have been testing various therapeutic agents in undulant fever, seeking some form of therapy that would clear the blood of organisms and eliminate the profound exhaustive period that followed the patient's recovery from the acute stage. Many patients with undulant fever recover within a relatively short period of simple symptomatic treatment such as complete bed rest until the temperature has been normal for two weeks, wholesome food and vitamins. Eight patients were so treated during 1945 and 1946, and there were six recurrences. This form of therapy had little effect in reducing the patient's exhaustive convalescent period. The mortality rate of undulant fever has always been regarded as very low, that is, about 3 per cent. However, at the onset of a patient's illness there are no means of forecasting the outcome.

In 1945, when the new antibiotic, streptomycin, was announced, experimental studies indicated that this agent was effective in inhibiting the growth of gram-negative organisms, including brucella. Through the kindness of the Committee on Chemotherapy of the National Research Council, five patients with acute undulant fever were treated with streptomycin between April and September, 1946; and since then a sixth patient has been treated. All of these cases had positive cultures before treatment was started. Blood cultures were obtained daily during the treatment phase and for several days after the completion of streptomycin therapy. Not all of the blood cultures became negative during the treatment phase. In three patients, the blood cultures became negative twenty-four to forty-eight hours after beginning treatment and remained consistently negative during treatment. In three the blood cultures remained intermittently positive during treatment; but in all of them the blood was cultured at weekly intervals after the patient's hospital discharge, for a four-week period, and the blood cultures were negative in each instance. The routine blood examinations were made at the Iowa Lutheran Hospital, Des Moines, Iowa. The blood culture studies were made in Dr. I. H. Bort's laboratory, University of Iowa, Iowa City, Iowa. During the previous year the National Research Council published reports[2,3] of cases of undulent fever treated with streptomycin. They stated that too few cases had been studied to permit any conclusions; however, they expressed the opinion that streptomycin did not strikingly alter the course of the disease in the cases studied. The six patients whom I treated with streptomycin were actually ill with

undulant fever. All of them received daily 500 mg of ascorbic acid intravenously while being treated with streptomycin. Huddleson[4] has indicated that the ascorbic acid level in the blood should be kept as high as possible, since the complement seems to be low during this disease and administration of the vitamin serves to maintain the complement at a high level. There were no chronic cases in this series.

### CASE REPORTS

CASE I. N. C., a colored male, age thirty-four, showed positive agglutination tests (1/1280) for Br. suis infection; tests for typhoid fever and tularemia were negative. Streptomycin treatment was started on the ninety-eighth day of the patient's illness, March 27, 1946. The patient responded immediately to streptomycin. The antibiotic was discontinued on the one hundred third day of illness, April 1st, 1946. This patient received a total of 20 Gm. of streptomycin. There were no reactions to the antibiotic. The blood cultures were positive on the ninety-fifth and ninety-sixth day of the illness, contaminated on the ninety-seventh day, negative on the ninety-eighth and ninety-ninth, positive on the one hundredth and one hundred first day, negative on the one hundred second and positive on the one hundred third to one hundred fifth day inclusive. Unfortunately, no blood cultures were obtained after the patient's discharge from the hospital. The patient returned to his occupation on May 20, 1946. This day would represent the one hundred fifty-sixth day since the onset of his illness.

*Comments.* This was the first patient treated with streptomycin. There were no recurrences of the disease and the clinical response in this patient was satisfactory. In view of our present knowledge, this patient should have been given a larger total dose of streptomycin.

CASE II. R. B., a colored male, age twenty-nine, had a blood culture taken on February 19, 1946, which was positive for Br. abortus. Agglutination tests taken on the same day were positive for brucellosis 1/1280 and negative for typhoid fever and tularemia. This patient was treated symptomatically at his home from February 16 to April 1, 1946. The "nonspecific" treatment had no effect upon his symptoms or the course of the disease. The patient was hospitalized on the fifty-first day (April 1, 1946) of his illness. He was then given the combined sulfathiazole-penicillin therapy. The blood sulfonamide level was maintained at 4 Gm. per 100 cc. and 40,000 units of penicillin were given intravenously, every three hours. The patient received this treatment for a seven-day period. Daily blood cultures were negative with one exception. This therapeutic measure was unsuccessful since there was a recurrence of the disease immediately following the patient's discharge from the hospital. On April 24, 1946, the patient re-entered the hospital. Streptomycin was started on the ninety-fourth day of his illness. The blood culture was positive on the ninety-third day and negative from the ninety-fourth to the one hundred third day. Streptomycin was discontinued on the one hundred second day of illness. Blood cultures on the one hundred fourth and one hundred fifth day of illness were positive. The patient's reaction to streptomycin was first apparent on May 27, 1946, by recurrence of the fever, oliguria on May 29th, and a skin rash on May 30th. The blood urea nitrogen, May 29, 1946 was 42.3 mg. per 100 cc. blood. The urine gave a positive reaction for sugar on May 26th, 27th and 30th. Streptomycin was discontinued on the one hundred second day of his illness because of the reactions. The reactions immediately ceased when the antibiotic was discontinued. The total parenteral (intramuscular) dose of streptomycin was 38 Gm. Blood cultures were obtained at weekly intervals after his hospital discharge. All cultures were negative and there were no further recurrences of brucellosis.

*Comments.* Recovery was complete and uncomplicated. A total of twenty-six blood cultures were obtained from this patient during his treatment and convalescent stage.

CASE III. R. T., a white male, fifty-four years of age, had a blood culture taken on April 5, 1946, and Br. suis was isolated. On the same day agglutination tests were positive for brucellosis 1/640 and negative for typhoid fever and tularemia. Streptomycin therapy was started on the patient's one hundred forty-fourth day of illness (May 24, 1946). He received a total of 33 Gm. of streptomycin. The antibiotic was discontinued on the seventh treatment day because of reactions. Traces of albumin first appeared in the urine on the third day of treatment and remained present until the drug was discontinued. Hyaline casts and red blood cells were also present in the urine during this four-day period. The test for sugar was positive during the same period that albumin was present in the urine specimen. The blood urea was 25.3 mg. on the sixth treatment day, 25 mg. on the eighth treatment day, 17.4 mg. two days after the streptomycin was discontinued, and 15.0 mg. two days later. A skin eruption first appeared twenty-four hours after streptomycin had been discontinued; however, the rash completely disappeared four days later. Blood cultures were obtained at weekly intervals (for a four-week period) after the patient's hospital discharge. These cultures were negative.

*Comments.* The patient had no recurrence of the disease and there were no remaining after-effects from the streptomycin reactions.

CASE IV. K. W., a colored male, age thirty-six, was treated symptomatically at his home from June 27 to June 29, 1946. His temperature fluctuated between 100° and 104.6°F. during that period. The blood culture was positive for Br. suis. Agglutination tests on June 17, 1946, were positive for undulant fever 1/320 and negative for typhoid fever and tularemia. The patient entered the hospital on June 30, 1946, the twenty-second day of his illness. Streptomycin was started on the twenty-fourth day. Reactions were noted early after medication was started. On the first day, the temperature reached 105.4°F. and on the second day there was a chill. The chill might have been related to the disease and unrelated to the streptomycin. Faint traces of albumin were consistently present in the urine during the treatment phase. Crystals were also noted in the urine specimen during this period. There were no other reactions to the antibiotic. The blood urea nitrogen was always within normal limits. The patient received a total of 51 Gm. of streptomycin between the twenty-fourth and thirty-fourth day of his illness. He was also given 400,000 units of penicillin between the thirty-fourth and thirty-fifth day of his illness. Blood culture reports were as follows: positive on the day that streptomycin treatment was started, negative on the third, fourth, seventh and eighth days, positive on the ninth day, negative on the tenth and eleventh days, positive on the first and second days after streptomycin was discontinued, and negative on the third day following treatment.

*Comments.* The patient's clinical response to streptomycin was considered to be satisfactory in this case. There were no recurrences of the disease. The patient returned to his work on August 20, 1946, which would represent approximately the seventy-third day after the onset of his illness.

CASE V. H. F., a white male, thirty-five years of age, had a blood culture taken which showed the presence of Br. suis. Agglutination tests on August 7, 1946, were positive for undulant fever 1/1280 and negative for typhoid fever and tularemia. The patient was first seen on the fifteenth day of his illness. The case was referred to me by Dr. N. Boyd Anderson. The patient's temperature on the fifteenth and seventeenth day of his illness varied from 96.8 to 105.8°F. Sulfathiazole-penicillin was started the eighteenth day of the patient's illness. The patient's blood culture was unknown at that time and I was awaiting permission from the N.R.C. to start streptomycin. This therapy was discontinued on the twenty-first day of the illness and streptomycin treatment was started on the same day. There were no reactions to the antibiotic. The daily blood cultures became negative twenty-four hours after streptomycin was started, and they remained consistently negative.

*Comments.* The patient received a total of 50 Gm. of streptomycin. The clinical results were excellent and there were no recurrences of the disease.

CASE VI. P. B., a white male, age forty-three, had a blood culture taken which showed the presence of Br. suis. Agglutination tests were positive for undulant fever 1/320, negative for typhoid fever and weakly positive for tularemia 1/80. The patient was treated symptomatically for a two-week period. Sulfathiazole-penicillin therapy was started on the twenty-first day of the patient's illness. This form of therapy was discontinued on the twenty-sixth day because of the patient's sensitiveness to sulfathiazole. Streptomycin therapy was started on the twenty-seventh day of the patient's illness. The patient received only 30 Gm. of the antibiotic because of the high cost of this form of therapy. Blood cultures were obtained daily and these became negative twenty-four hours after the treatment was started. There were fifteen blood cultures in all. The cephalin-cholesterol flocculation test was positive before the streptomycin was started and negative at the completion of therapy.

*Comments.* The clinical results were excellent; however, the patient developed a severe generalized eruption over his entire body. An attending dermatologist diagnosed the condition as erythema multiforme bullosum and said that sulfathiazole was probably responsible for the skin complication.

*Streptomycin Dosage.* The total dose of the antibiotic varied for each patient. The daily dosage was 5 Gm., intramuscularly in divided doses of 0.625 Gm., every three hours. Normal saline was used as a diluent. The first patient received 20 Gm. of streptomycin. The second received 38 Gm. but streptomycin was discontinued because of reactions. The third patient received 33 Gm. but the antibiotic was again discontinued because of reactions. The fourth patient received 51 Gm., and the fifth received 50 Gm. The sixth received only 30 Gm.

*Laboratory Data in Each Case.* Daily red and white blood determinations, blood cultures, and urinalyses were obtained. Every other day blood urea nitrogens and sedimentation rates were done. Hanger's cephalin flocculation test was made in the sixth case at the beginning and at the completion of streptomycin therapy.

*Reactions to Streptomycin.* This new antibiotic should be used with care and patients should be closely observed while receiving this form of therapy. In the present series, no patients developed eighth cranial nerve involvement; however, the routine laboratory tests indicated possible injury to the liver and kidney. The urinary crystals observed were undoubtedly the results of the action of streptomycin upon the kidney, and not streptomycin crystals. This latter is my personal assumption. The reactions promptly disappeared when streptomycin was discontinued. The antibiotic was immediately stopped as soon as a severe reaction appeared.

## SUMMARY

Our series of six cases is too small to formulate any final conclusions. The experiments were interesting and the results were very encouraging.

In the past, our therapy has been unsatisfactory for two reasons: (1) There were too many recurrences of the original infection, usually from two to five, and (2) extremely prolonged, exhaustive convalescent stage that followed the patient's apparent recovery from the acute phase of his illness; this period varied from four to twelve months. In the six patients treated with streptomycin the following favorable factors were noted: (1) There was an immediate decrease in the elevated temperature. (2) There was an elimination of subjective symptoms (chills, sweats, anorexia, muscle weakness) and earlier return of appetite. In the past I have always regarded the appearance of a ravenous

appetite as a good omen. (3) There were no recurrences or relapses of the infection after the antibiotic was discontinued. (4) There was a marked decrease in the length of the convalescent stage. This was a very significant factor. Convalescence in the streptomycin-treated patients did not extend beyond a sixty-day period.

## CONCLUSIONS

I believe that streptomycin is an excellent therapeutic agent for the treatment of acute undulant fever. All six patients, as previously explained, responded better to this new form of therapy than to any other therapeutic measure used in the previous nineteen years. In this series of six cases, five were of the Brucella suis and one of the Brucella abortus strain. There were no cases of the Brucella melitensis variety.

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# Toxicity of Streptomycin*

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THE toxicity of a chemotherapeutic agent cannot be properly considered apart from the diseases for which it is to be used. Virtually any drug, on occasion, may produce untoward reactions in certain individuals. Evaluation of toxicity, therefore, consists principally in determining the relative dangers of drug and disease. The infections in which streptomycin therapy is of benefit are discussed in the other papers of this symposium. It is against that background of the potential dangers of these individual diseases that the subsequent discussion should be considered.

The problem of the toxicity of streptomycin is complicated by the fact that the preparations which have been in clinical use have varied widely from extremely crude to highly purified substances. Thus, it has not always been possible to establish whether a particular manifestation of toxicity was produced by the antibacterial agent itself or resulted from associated impurities. In a study, which is published elsewhere,[1] an attempt has been made to define the respective rôles of antibacterial agent and impurities by the long continued administration of highly purified streptomycin sulfate to a group of seventeen tuberculous individuals. Subsequent to the study, approximately forty additional patients with tuberculosis have been treated on the same regimen (3.0 Gm. daily) with the same preparation of streptomycin for periods of two to four months. The highly purified streptomycin was prepared from crystalline material* and is estimated to be at least 95 per cent pure. This experience, together with similar experience with less purified streptomycin, forms the basis of the present discussion.

The untoward reactions which various investigators,[2-9] have observed during the administration of streptomycin are of five general types: (1) the so-called "histamine" reaction; (2) irritation at the site of injection and on topical application; (3) various manifestations of anaphylaxis; (4) evidences of renal irritation occasionally accompanied by impairment of renal function and (5) a neurologic disturbance characterized by vestibular dysfunction and occasionally by deafness.

## HISTAMINE REACTION

The so-called histamine reaction is largely of historic interest, as the substance responsible for its occurrence is no longer present in the preparations of streptomycin which are available for clinical use. The reaction would appear shortly after the intravenous or intramuscular administration of certain lots of streptomycin and was characterized by flushing, headache and an abrupt fall in arterial pressure. The resemblance between the reaction and the phenomena produced by an injection of histamine and the fact that histaminase-treated streptomycin would no longer produce the reaction in animals,[10] constitute the basis for the implication of histamine. The complete

* A part of the highly purified streptomycin was supplied by the National Research Council Committee on Chemotherapeutics and Other Agents, Dr. Chester S. Keefer, chairman, and the remainder was generously donated by Charles Pfizer and Company, Brooklyn, N. Y.

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absence of this reaction, following the administration of the partially purified streptomycin in general use during 1946 and 1947, indicates that this manifestation of toxicity was produced by a contaminating substance.

### LOCAL IRRITATION

The intramuscular administration of partially purified streptomycin may, on occasion, give rise to a considerable degree of soreness and induration at the site of injection. There does not seem to be any difference between the sulfate or the hydrochloride salts of streptomycin in the production of this local irritation. Moreover, it would not appear as if the choice of vehicle, distilled water or isotonic saline, plays a significant rôle in the phenomenon. It is virtually certain that pain and soreness at the injection site are caused by adventitious substances which can be removed by a high degree of purification. The highly purified material produced no more local reaction on intramuscular administration at three-hour intervals for 120 days than is observed from the comparable administration of the most highly purified preparations of penicillin in current use.

### TOPICAL APPLICATION

*Intrathecal Administration.* The intrathecal administration of 0.05 to 0.1 Gm. of partially or highly purified preparations of streptomycin to individuals with or without central nervous system disease is usually well tolerated. Occasionally, particularly when relatively impure material is used, the intrathecal administration of such doses is followed by headache, vomiting and a moderate increase in the number of cells in the cerebrospinal fluid. For this reason it is advisable to use the most purified material available when streptomycin is to be administered by the intrathecal route. It is probable that the *repeated* intrathecal instillation of streptomycin does produce a slight degree of irritation.

Not infrequently, the patient will complain of pain over the sacrum and posterior thighs during the twelve to twenty-four hours immediately following intrathecal treatment. Usually this symptom disappears after one or two weeks of intrathecal therapy even though the latter is continued.

A sustained pleocytosis in the neighborhood of 200 to 900 cells per cu. mm. is customarily present in the cerebrospinal fluid of individuals with tuberculous meningitis throughout the entire period of intrathecally administered therapy. One or two weeks after the cessation of such therapy, the total cell count usually approaches or attains normal values without appreciable changes in the other components of the fluid. The degree of such irritation must be slight, however, for postmortem examination of four individuals who had received 20 to 100 intrathecal injections of the highly purified streptomycin failed to reveal any evidence suggestive of local irritation in the meninges or brain.

The intrathecal administration of doses larger than 0.1 Gm. (e.g., 0.2 to 0.4 Gm.) may be associated with the appearance of definite signs of toxicity even though highly purified streptomycin is used. Within less than an hour after the treatment, headache, vomiting and nystagmus may appear. During the ensuing twenty-four hours the patient is somnolent and occasionally may be semistuporous. Respirations may be slowed and transient retention of urine in the bladder may occur. During the second twenty-four hours after the intrathecal instillation the evidences of toxicity usually disappear completely. Thus far, no instances of transverse myelitis have been observed. In at least several individuals, however, the repeated intrathecal administration of 0.2 to 0.4 Gm. streptomycin (partially purified) has been associated with

the appearance of delirium which in one instance[11] resembled a Korsakoff's psychosis. In these individuals, the evidences of cerebral involvement slowly disappeared after cessation of streptomycin therapy.

It is possible that accumulation of the drug after repeated administration may be partly responsible for these neurologic reactions. Bio-assay of the cerebrospinal fluid twenty-four to seventy-two hours after an intrathecal injection of 0.2 to 0.4 Gm. of streptomycin usually reveals the presence of an appreciable concentration of the drug.

As streptomycin is administered intrathecally only in the presence of central nervous system infection, it is difficult and frequently impossible to decide whether particular clinical manifestations such as described above represent the results of infection or toxicity. Therefore, when such phenomena are encountered, it is advisable to interrupt the intrathecally administered therapy for a period of several days to a week and to resume therapy only with caution. Moreover, at the present time it would appear that the single dose of 0.1 Gm. for intrathecal administration to an adult should not be exceeded.

*Topical Use Other Than Intrathecal.* An extensive experience has not yet been accumulated on the instillation of streptomycin into body compartments other than the subarachnoid space. From isolated observations, however, it would seem that the introduction of a 1 per cent solution of streptomycin (partially or highly purified) into the pleural or peritoneal cavities is well tolerated.

## MANIFESTATIONS OF ANAPHYLAXIS

Phenomena which presumably represent manifestations of anaphylaxis are encountered with greater frequency during the administration of streptomycin than during treatment with the sulfonamides or penicillin. Usually, however, it is not necessary to discontinue streptomycin therapy because of these reactions. Three general types of presumed anaphylactic phenomena have been observed: fever, dermatitis and eosinophilia. Although all three types of reaction are frequently present together, each may appear as an isolated phenomenon.

*Fever.* A sustained fever of considerable degree (102° to 104°F.) may occur as an apparent reaction to the administration of partially purified streptomycin. It is by no means certain that sustained fever of this type is a manifestation of anaphylaxis. It is unlikely, however, that such fever reflects the presence of pyrogens in the particular preparation of drug used, for the fever does not usually appear until after five to seven days of therapy. As with drug fevers of other origin the sustained fever of streptomycin therapy is characterized by: (1) the fact that the patient appears much less ill than would be anticipated from the height of the fever; (2) an absence of collateral signs of infection notably leukocytosis and (3) abrupt defervescence after cessation of therapy. It is of interest that fevers of this character have not been observed as yet following the use of highly purified streptomycin.

*Dermatitis with or without Fever.* In a small number (perhaps 5 per cent) of the individuals who receive streptomycin a definite eruption will appear during the second or third weeks of therapy. The rash is identical with the toxic eruptions caused by many other chemotherapeutic agents and may be morbilliform, maculopapular or merely a blotchy erythema. It is usually pruritic and may progress to a superficial scaling dermatitis accompanied by periorbital edema and enlargement of the lymph nodes. The intensity of the constitutional symptoms which may accompany such a reaction varies considerably. In some instances the appearance of the erup-

tion is associated with an influenza-like syndrome with fever, headache, nausea, vomiting, pains in the muscle joints, leukopenia and eosinophilia. Occasionally, at the height of the reaction there is an abrupt fall in arterial pressure. The latter phenomenon is distinct from the histamine reaction described previously and is apparently similar to the nitritoid reaction which is observed during therapy with certain organic arsenicals. In the streptomycin reaction the arterial pressure usually returns to the normal range within a few hours. If streptomycin therapy is discontinued, the constitutional symptoms usually disappear completely within twenty-four hours and the eruption fades during the succeeding week.

In the majority of the patients who develop toxic eruptions, however, the constitutional symptoms are minimal or absent and the principal phenomena are pruritus and eosinophilia. In these individuals the continued administration of the streptomycin is usually associated with a persistence of the itching. Although the latter may be relieved considerably by the use of antihistamine agents such as pyribenzamine or benadryl, the symptom usually persists as long as the patient continues to receive streptomycin.

In addition to these individuals who present frank dermatologic evidence of anaphylaxis, another group, probably equal in size, develop questionable phenomena, which consist of such findings as an ephemeral itching eruption localized to an antecubital fossa or a transient conjunctivitis. It is impossible to be certain that such trivial clinical phenomena are related to the administration of the streptomycin. As with the overt eruptions, however, these trivial and ephemeral rashes usually appear during the first three weeks of therapy and are accompanied by eosinophilia.

*Eosinophilia without Eruption.* In addition to the individuals who develop eosinophilia in the course of a definite or questionable eruption, a number develop eosinophilia without other evidence of drug sensitization. It is impossible at present, to estimate the precise incidence of this phenomenon but it is apparently high particularly among those individuals who receive streptomycin therapy for several months. Eosinophilia of 5 per cent or more appeared at some time during the four months of therapy in fourteen of the first sixteen patients who received highly purified streptomycin. In nine of these individuals the phenomenon did not appear until the second or third months of therapy.

The eosinophilia varies from an intermittent phenomenon present for one or two weeks at a time, to a constant finding which persists as long as sixty to a hundred days. In general, the eosinophilia ranges between 10 and 15 per cent but not infrequently may be sustained between 25 and 40 per cent for as long as four or five weeks. The percentage of eosinophiles usually falls to within the normal range during the month succeeding the cessation of streptomycin therapy.

In the study of highly purified streptomycin, there was one instance in which sustained eosinophilia was accompanied by an acute synovitis which involved the proximal interphalangeal joints of the hands and feet. As the joint symptoms largely subsided despite continuation of streptomycin therapy the relation of the synovitis to the drug is questionable. Other than this (and save for the eruptions mentioned previously) the eosinophilia observed during the administration of either partially or highly purified streptomycin has not been accompanied by symptoms suggestive of diffuse vascular disease.

*Continuation of Therapy in the Presence of Manifestations of Anaphylaxis.* From available experience with streptomycin it is probable that in most instances no imme-

diately serious situation would be precipitated by continuing streptomycin therapy in the presence of evidences of anaphylaxis. It is not yet established, however, that the sensitivity reactions observed with the use of streptomycin and other chemotherapeutic agents, are transient phenomena completely free from implications concerning the patient's future health. Until the exact significance of drug sensitivity reactions can be established it is advisable to regard them as potentially dangerous and as indications for a complete revaluation of the relative dangers of drug and disease. Thus if the patient is acutely ill or has an infection which continues to constitute a definite threat, it is proper to continue streptomycin therapy despite evidences of anaphylaxis. Conversely, if the infection for which therapy was instituted has largely subsided and relapse is not anticipated, it is advisable to discontinue the antibacterial treatment. There are situations, particularly in the treatment of tuberculosis, in which although the infection carries no immediate threat, it is undesirable to discontinue streptomycin therapy permanently. In such a situation, when manifestations of anaphylaxis appear, it is proper to discontinue therapy and to administer single test doses of streptomycin at weekly intervals. Therapy may be resumed (usually within three to four weeks) when the test doses no longer evoke evidences of drug sensitivity.

### RENAL FUNCTION

The administration of streptomycin is not infrequently accompanied by cylindruria and occasionally by a minimal degree of albuminuria. On the basis of the experience thus far, it would not appear that these findings represent an important manifestation of toxicity. In a small number of individuals, however, (perhaps 1 to 3 per cent) the administration of streptomycin is associated with a significant reduction in renal function accompanied by an increase in the concentration of urea nitrogen in the blood. Moreover, the writer has observed one instance of a fatal nephrosis which was apparently produced by the administration of partially purified streptomycin. It should be emphasized, however, that in virtually all instances observed thus far in which significant impairment of renal function has appeared during therapy, overt or probable renal disease had existed before streptomycin treatment was started.

The apparently benign cylindruria is present sporadically during streptomycin therapy and may appear within forty-eight hours of the initiation of treatment. Granular, hyaline and occasionally cellular casts may be excreted. The number of casts varies from a few to as many as fifteen or twenty per low powered field of a centrifuged specimen. The intensity of the cylindruria varies directly with the degree of acidity of the urine. If a neutral or slightly alkaline urine is excreted the cylindruria is minimal or absent. Conversely the cylindruria is accentuated if a highly acid (pH 4.5 to 5.0) urine is elaborated. Cylindruria which is present during the latter part of a course of streptomycin therapy disappears promptly with the cessation of treatment. Although a minimal degree of albuminuria may accompany the cylindruria, hematuria definitely attributable to streptomycin has not been observed.

The nitrogen retention and reduced renal function (urea clearance) which occurs in a small number of treated patients presumably represents a more advanced form of the same process which produces the sporadic cylindruria. The reduction in the urea clearance and the retention of nitrogen usually do not appear until after several weeks of streptomycin therapy. Usually, though not invariably, the renal impairment is accompanied by a moderate degree of albuminuria and cylindruria. The exact

nature of the process is by no means clear. In one instance observed by the writer a reduction in urea clearance to 40 per cent and an increase in blood urea nitrogen to approximately 25 mg. per 100 cc. occurred during the first month of streptomycin therapy and were maintained for approximately three months. Despite the continuation of therapy, however, during the fourth month the values for the urea clearance and blood urea nitrogen slowly returned to normal range. In another individual the urea clearance fell to 20 per cent and the blood urea nitrogen rose to approximately 45 mg. per 100 cc. at the end of a sixty-day course of streptomycin therapy. These values remained essentially unchanged during the four months following the cessation of treatment and during a subsequent ninety-day course of streptomycin therapy.

The instance of fatal nephrosis mentioned previously occured in a forty-two year old woman who received 4 Gm. of partially purified (1945) streptomycin daily as treatment for a moderately severe typhoid fever. On the fourth day of therapy she developed hemoglobinuria and anuria which terminated fatally approximately twenty-four hours later. At necropsy a severe disseminated necrosis of the convoluted tubules and extensive arteriolosclerosis were present. The tubular necrosis was similar to that seen after the administration of mercuric chloride, uranium nitrate or potassium dichromate. There were no changes in the kidneys which resembled the lesions of typhoid fever. It was considered probable that the observed nephrosis represented a toxic effect of streptomycin on previously damaged kidneys. It should be emphasized that such serious reactions must be rare, for in the treatment of urinary tract infections streptomycin is frequently administered in the presence of renal insufficiency without producing further impairment of renal function.

On the basis of admittedly incomplete information the situation in regard to renal damage from streptomycin may be summarized as follows: (1) Both partially purified and highly purified preparations of the drug give rise to sporadic cylindruria in a large number of instances. This phenomenon is apparently benign, can be largely prevented by the maintenance of an alkaline urine, and is not an indication for the interruption or cessation of streptomycin therapy. (2) In a small number of individuals, chiefly those with pre-existing renal damage, the administration of streptomycin results in a reduction in renal function and an elevation of the blood urea nitrogen. In at least some of these individuals the process is reversible. Until the problem is more clearly defined, however, it is advisable to regard a rising urea nitrogen as a definite indication for either the cessation of therapy or the reduction of dosage to no more than 1 Gm. daily. An additional reason for caution in the presence of renal insufficiency is the possible relationship between the retention of streptomycin and the development of deafness which is discussed below.

## NEUROLOGIC REACTIONS

The neurologic reactions are undoubtedly the most important toxic reactions to streptomycin and constitute virtually the only serious handicap to the prolonged use of the drug. There are two types of reaction: vestibular dysfunction, which occurs frequently, and impairment of hearing which develops only rarely.

*Vestibular Dysfunction.* The onset of this reaction appears to bear a definite relationship to the size of the daily dose and the duration of treatment. In general, the reaction appears at the end of the fourth week on a 1 or 2 Gm. daily dose; at the end of the third week on a 3 Gm. daily dose and during the second week on larger doses. When a small daily dose (1 or 2 Gm.) is adminis-

tered for only seven to ten days, the reaction does not usually become clinically evident at all. Vestibular dysfunction appears with the same uniformity and apparently the same degree of severity after the use of either partially purified or highly purified streptomycin.

The reaction is characterized by the appearance of headache or a sensation of "heaviness in the head" which disappears within twenty-four hours and is followed by the development of a sensation which resembles vertigo. The symptom differs from vertigo in that a rotary component is lacking. The afflicted individuals experience a sensation of "overshooting the mark" when a sudden movement is made. For example, immediately after completing the movement of rolling over in bed, the patient feels as if he is continuing to roll over and over. On reaching for an object he feels as if his hand is progressing three or four inches past the object although past-pointing is not actually present. Occasionally, the patient will note that there is a momentary delay in focusing the eyes after a sudden change in position.

There is a considerable variation in the degree of vestibular dysfunction noted by different individuals on the same regimen of dosage. In approximately one-third of the patients (who receive a streptomycin for one month or more) the reaction is negligible and discovered only by careful questioning. In the remainder, the disorder is moderately severe or severe. In such instances, at the peak of the reaction, the patients are unable to walk or to sit up in bed unassisted and may be acutely uncomfortable even while lying flat. Nausea is likely to be produced by change in position and may be accompanied by vomiting. The symptoms usually persist in acute form for seven to ten days and then subside to the point where only an unusual stimulus such as a sudden shaking of the head would produce the symptoms momentarily. Some individuals, however, although symptom-free while sitting erect in bed, may have difficulty when an ambulatory regimen is resumed. In the majority of instances the symptoms of minimal vestibular dysfunction persist for approximately sixty to ninety days and then disappear except when the individual attempts to walk in complete darkness. A minority of those afflicted (precise number not yet established) have some difficulty in walking even in the daylight for as long as six or eight months after the acute reaction. Usually, however, as long as the individual can orient himself visually, he can walk without obvious ataxia. It should be noted that such individuals do not have to watch their feet while walking but unconsciously maintain their balance by orienting themselves to any fixed objects.

Nystagmus appears in association with the vestibular dysfunction in surprisingly few instances. With the use of quantitative technics for caloric stimulation it is usually possible to demonstrate hypofunction of the vestibular apparatus which persists for many months after the acute reaction.

The mechanism by which the vestibular dysfunction is produced is not known and presumably the site of the lesion may be either in the labyrinth or in the brain. There is evidence which suggests that at least part of the dysfunction is in the nature of an intoxication which is reversible up to a certain point, but which results in more persistent damage if the administration of streptomycin is continued. For this reason it is advisable to discontinue streptomycin at the first sign of dysfunction, or preferably to stop therapy before the time at which the reaction customarily appears.

If the nature of the infection which is being treated is such that the cessation of therapy is inadvisable, symptomatic recovery, as described above, will occur despite the continued administration of streptomy-

cin. It should be realized, however, that such immediate recovery apparently represents the activation of compensatory mechanisms and does not reflect a return of vestibular function. As would be anticipated, the degree of compensation varies among individuals and may be appreciably less complete in elderly individuals. It is not known whether any degree of vestibular (i.e., not merely symptomatic) recovery is to be expected in those individuals whose dysfunction has persisted for many months after the cessation of therapy. From a few isolated observations[12] there is reason to hope that in some instances at least, true functional recovery may be possible.

*Deafness.* In the Cornell–New York Hospital series, bilateral nerve deafness ranging between 50 and 100 per cent in extent, occurred in seven of the first one hundred patients who received streptomycin. The reaction occurred following the use of the highly purified streptomycin as well as after administration of the less pure material. The significance of this reaction, in terms of the toxicity to be expected from streptomycin, is much less alarming, however, than is suggested by this relatively high incidence. Five of the seven individuals had tuberculous meningitis and had received prolonged streptomycin therapy by the intrathecal route. The two patients who became deaf in the absence of meningitis (or intrathecal therapy) had marked renal insufficiency which resulted in the persistence of unusually high concentrations of streptomycin in the blood. Moreover, aside from these two types of cases, deafness was observed in the Mayo Clinic series only in patients who received unusually large doses of streptomycin (5 to 10 Gm. daily). Thus in the combined Mayo Clinic and Cornell–New York Hospital series, deafness has appeared in only three types of cases: (1) individuals who have received unusually high daily doses; (2) individuals who have received 1 to 4 Gm. daily in the presence of marked renal insufficiency; (3) individuals (with tuberculous meningitis) who have received streptomycin intrathecally.

The limitation of the reaction to these three types of cases strongly suggests that the development of deafness during streptomycin therapy is largely a result of overdosage. To be sure, if an excessively large dose of a drug can produce a reaction such as deafness in some patients, it is to be anticipated that some unusually susceptible individual will develop the same reaction on what is ordinarily considered to be a small dose of the drug. On the basis of present experience, however, it would seem that deafness as a result of therapy represents only a small hazard to patients with normal renal function who receive only 1 to 3 Gm. of streptomycin each day by the intramuscular route. In some instances, the deafness which may appear in the course of meningitis is presumably caused by the infection and not by intrathecally administered streptomycin. It is reasonable to assume, however, that the introduction of such relatively large quantities of streptomycin directly into the subarachnoid space contributes to the development of deafness.

Because of the possibility of deafness, it is advisable to obtain an audiometric examination on all patients who are to receive streptomycin. The examination should be repeated routinely at fortnightly or monthly intervals and even more frequently in the presence of meningitis or impaired renal function. If any reduction in hearing develops, streptomycin should be discontinued immediately save in the presence of an infection which is customarily fatal in the absence of antibacterial therapy. Brown and Hinshaw[9] have observed that the presence of a constant, roaring, low-pitched tinnitus frequently precedes the appearance of deafness. High-pitched, intermittently present tinnitus, is so ubiquitous a symptom with or

without streptomycin therapy, that its value as a warning of incipient deafness is questionable.

From the preliminary studies of Stevenson, Alvord and Correll,[13] it appears that the site of toxic action which results in deafness is in the brain. These investigators noted liquefaction necrosis of the ventral cochlear nucleus in the tissues of three patients of the New York Hospital series who had developed deafness during therapy with highly purified streptomycin. Similar lesions were also found in the brain of one dog who had received intensive treatment with partially purified streptomycin. It is of interest that in the brain of one of the patients the same type of lesion was present in the vestibular nuclei, which suggests that the site of the vestibular toxicity is also centrally located.

There has not yet been sufficient experience to permit an estimation of the degree of recovery of hearing which is to be anticipated in those patients who have suffered a reduction in hearing during therapy. About all that can be said is that in some instances considerable improvement (30 to 50 per cent) has occurred. Presumably, however, in many instances the loss of hearing is permanent.

Other than the reactions involving vestibular or cochlear function, no effects of streptomycin upon the nervous system have been noted.

### MISCELLANEOUS MANIFESTATIONS OF TOXICITY

Leukopenia (1,500 to 3,000 cells per cu. mm.) occasionally accompanied by a relative granulocytopenia has been observed during the course of streptomycin therapy. The few cases in the Cornell–New York Hospital series were all in patients with acute hematogenous tuberculosis, a condition in which involvement of the bone marrow is not uncommon. Despite the continuation of streptomycin therapy, the total leukocyte counts eventually rose to within the normal range. In the event that granulocytopenia should be observed in the absence of miliary tuberculosis it would be advisable to consider it as a manifestation of toxicity and an indication for the immediate cessation of streptomycin therapy.

One instance of thrombocytopenia has been observed in a patient with acute brucellosis who was receiving 6 Gm. of streptomycin daily.[14] Recovery was prompt and complete after the discontinuance of therapy.

No evidence has been obtained which would indicate that the administration of streptomycin results in anemia or in damage to the liver.

### SUMMARY

The administration of streptomycin by the intramuscular route in a daily dose between 1 and 3 Gm. is well tolerated for a one or two-week period by most individuals. With the single exception of vestibular dysfunction the same dose regimens are well tolerated by most individuals for periods as long as four months. Although daily doses larger than 3 Gm. are apparently well tolerated by some individuals for short periods of time, it is probable that 3 Gm. represents the upper limit of the safe daily dose.

The histamine reaction, irritation at the site of injection and possibly the sustained febrile reactions are not caused by streptomycin but by impurities which are removable with refinements in the process of manufacture. All of the other manifestations of toxicity which have been observed after the use of impure streptomycin have also occurred during the administration of highly purified preparations of the drug.

The toxicity of streptomycin is sufficiently low to justify the use of the drug in serious or potentially serious infections. Con-

versely, the incidence of toxicity, notably vestibular dysfunction, is sufficiently high after several or more weeks of therapy, that the drug should not be used for infections with a generally favorable prognosis such as minimal pulmonary tuberculosis or chronic brucellosis.

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# Review

## Acute Coronary Artery Diseases

### *History, Incidence, Differential Diagnosis and Occupational Significance*

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ACUTE coronary artery disease did not suddenly appear in the twentieth century; it has existed for hundreds, probably thousands of years. There is evidence that it occurred among the early Egyptians. Ruffer[1] writing "On arterial Lesions Found in Egyptian Mummies (1580 B.C.–525 A.D.)" stated that the Egyptians of 3,000 years ago not only suffered from calcification of the arteries, but that the arteriosclerosis at that time was of the same nature as this disease today, that is, calcification following atheroma.

From his investigations, Ruffer concluded that the stress and strain of modern life, exertion, meat diet, tobacco, alcohol and syphilis are not contributory factors in the production of coronary disease. Previously reported observations of my colleagues and myself[2] support this conclusion. In a series of cases of acute coronary occlusion we could not find any precipitating factors, and believe that this disease is solely a sequel to arteriosclerosis of the coronary arteries.

Brim[3] has interpreted certain passages in the King James translation of the Bible from the standpoint of modern medicine and he believes that some of the accounts of sudden death represent acute coronary occlusion. For example, "In the case of Sichon the king of Cheschbon, the Lord hardened his heart, and closed his heart, and he was therefore delivered unto your power." (Deut. 2:30).

Reisman and Harris[4] point out an illustration of "instantaneous painless coronary death" to be found in Homer's Odyssey. "Phoebus Apollo shed down his gentle darts upon Prontis, son of Onetor, Manetaus' navigator, and he dropped dead with the steering oar of the moving ship within his hands."

Hoffman[5] writes that Hippocrates of Cos in his "Prognostics" said that "Cardiodynia which occurs more frequently in senility foretells sudden death."

Many a physician before Heberden[6] must have observed episodes of angina pectoris. Seneca[7] recorded his own suffering from this disease, as did the Earl of Clarendon.[8] But it was Heberden who, as the result of observation of a hundred patients in his daily practice, established the syndrome of angina pectoris as a clinical entity. His account written in 1768 reads like a recent textbook of the disease.

In spite of his knowledge of angina pectoris, Heberden did not realize that there was any relationship between this syndrome and disease of the coronary arteries. Credit must be given to Edward Jenner[9] and Caleb Parry[9] for the establishment of this connection. These authors did not publish their ideas until the death of their mutual friend John Hunter, because the latter was a victim of angina pectoris.

*Experimental Investigations.* While knowledge of the clinical manifestations of disease

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of the coronary arteries was accumulating, the experimental work which would eventually lead to the conception of the function of these vessels of the heart lagged behind. Chirac,[10] in 1698, reported that ligature of the coronary arteries in the dog produced a standstill of the heart. This observation is merely of historical interest for it bore no fruit. In 1698 there was no appreciation of the clinical importance of the coronary vessels.

In 1842, Hall[11] contended that ossification of the coronary arteries could cause a fatal outcome, and that abrupt obstruction would produce sudden death. To test this theory, Ericksen[12] conducted some experiments on animals. He concluded that arrest of the coronary circulation produced cessation of the heart's action and that an increase in the quantity of blood sent into or retained in the muscular fibers of the heart caused a corresponding increase in the activity of that organ.

Burns[13] compared the action of the heart supplied by calcified arteries with the action of a limb around which a ligature has been applied. "Exercise, passion, and ardent spirits" he considered a danger to a heart so affected.

In recent years, Keefer and Resnick[14] showed that anginal pain was due to anoxemia. Sir Thomas Lewis[15] was of the opinion that this pain was caused by accumulation of chemical poisons.

In 1935, Tennant and Wiggers[16] observed that immediately following occlusion of branches of the coronary arteries in dogs, the ischemic areas ceased to contract. Then the involved area bulged passively while the remainder of the ventricle contracted normally. This reversal of pulsation or "paradoxical" pulsation was observed fluoroscopically in man by Master and his co-workers.[17]

*Acute Coronary Artery Occlusion.* Coronary disease has been shown to have existed in ancient times and the association between angina pectoris and sclerosis of the coronary arteries was first made in the eighteenth century. The actual appreciation of acute coronary occlusion as a definite disease, that is, as a special form of coronary sclerosis, is of relatively recent development.

In 1878, Hammer[20] described an instance of coronary thrombosis in an article entitled, "A Case of Thrombotic Occlusion of One of the Coronary Arteries of the Heart." He diagnosed the condition before death in a patient who suffered sudden collapse accompanied by a ventricular rate varying from but 8 to 40 beats a minute. The heart sounds were faint. At autopsy a thrombus was found in the right sinus of Valsalva, closing the ostium of the coronary artery. This case is probably the first instance in which complete heart block in coronary occlusion is described.

In 1880, Winsor,[18] a physician who practised in Winchester, Massachusetts, presented a paper entitled, "Angina Pectoris with Rupture of the Heart." This author clearly recognized the relation of coronary thrombosis to preceding disease of the coronary vessels and realized that the myocardium became "degenerated" with rupture of the involved wall.

Huber[19] (1882) related necrotic and fibrotic lesions in the myocardium to atheromatosis of the coronary artery.

In "Some Notes on the Coronary Arteries" published in 1896, George Dock[21] reported a case in which antemortem diagnosis of coronary thrombosis was made in a man sixty-four years old.

In 1910, two Russians, Obratzow and Straschesko[22] discussed the clinical aspects, diagnosis and pathological anatomy of occlusion of the coronary arteries, and the consequent infarction and myomalacia of the heart.

Hochhaus,[23] in 1911, reported four instances of acute coronary artery occlusion,

two of which were correctly diagnosed before death with experience gained from the other two.

Not withstanding these early reports, knowledge of acute coronary artery occlusion did not become at all general until Herrick,[24,25] presented a complete clinical and pathological picture of this disease in his two brilliant reports published in 1912 and 1918. He showed that the coronaries are not strictly end-arteries, but that they develop functioning anatomic anastomoses; he discussed the symptoms of coronary thrombosis, the pericardial friction rub; he pointed out that occlusion of a large branch of a coronary artery or even of a main trunk need not necessarily cause sudden death.

In 1929, Levine[26] published his monograph, "Coronary Thrombosis." In this carefully detailed study was assembled all the available knowledge concerning coronary thrombosis, clinical electrocardiographic, pathological and therapeutic.

Fred Smith[27,28] and H. E. B. Pardee[29] first correlated the electrocardiographic observations with clinical evidence of acute coronary occlusion.

"*Acute Coronary Insufficiency*" (*without Acute Occlusion.*) Acute coronary occlusion is now a well recognized disease. Indeed, its features are so well marked that they have tended to obscure recognition of another, equally important product of coronary artery sclerosis, that is, "acute coronary insufficiency" (without acute occlusion) or myocardial ischemia or necrosis (infarction) without acute coronary occlusion. This condition, has been recognized in the German literature,[30–34] but only recently has its importance been appreciated in this country.[35–39] My colleagues and I have presented evidence to show that acute coronary insufficiency without acute occlusion is a disease entity with specific etiologic features, and characteristic pathologic and electrocardiographic patterns.[38–40] This condition is not however, sufficiently widely recognized, and the importance of differentiating acute coronary insufficiency without acute occlusion from acute coronary occlusion cannot be over emphasized.

Although acute coronary insufficiency (without acute occlusion) was not recognized as a disease entity until less than twenty years ago, the writings of some of the early physicians show a certain perception into the nature of this phase of arterial sclerosis. Parry,[9] for instance, in speaking of ossification of the coronary arteries noted that such a heart "may be fit" during a state of mental tranquillity, yet when any unusual exertion is required, its power may fail.

## MAGNITUDE OF CORONARY DISEASE

It has become clear that heart disease has been since 1912 the chief cause of death in this country.[41–44] In 1942, almost 400,000 persons died of cardiac disease alone, about 28.5 per cent of all deaths.[42] It is probable that at least 4,000,000 persons in the United States are afflicted with heart disease. One survey gives an estimate of double this figure, placing the total at 8,000,000.[45]

TABLE I

CAUSE OF DEATH FOUND IN POSTMORTEM EXAMINATION OF 489 CASES OF CARDIAC DISEASES—THE MOUNT SINAI HOSPITAL, N. Y. 1932–1938

| Period | No. of Cases | Acute Coronary Diseases Per Cent | Rheumatic Heart Disease Per Cent | Congenital, Luetic, Misc. Per Cent |
|---|---|---|---|---|
| 1932–36 | 310 | 45.0 | 26.0 | 29.0 |
| 1937–38 | 179 | 54.0 | 28.0 | 18.0 |

Various writers have reported that acute coronary diseases comprise 25 to 40 per cent of all heart diseases.[46] In an investigation of different types of cardiac diseases carried on between 1932 and 1938, careful postmortem

TABLE II*

| | Acute Coronary Insufficiency | Acute Coronary Occlusion |
|---|---|---|
| Synonyms | Acute coronary insufficiency without acute occlusion<br>Myocardial necrosis or infarction without acute coronary occlusion<br>Subendocardial necrosis or infarction | Acute coronary insufficiency with acute occlusion<br>Acute coronary thrombosis<br>Myocardial infarction due to coronary artery occlusion |
| Mechanism | Decreased supply of oxygen or blood to the myocardium or disproportion between the supply and the demands of the latter<br>Transient, slight, to prolonged and severe anoxia or ischemia<br>Reflex vasoconstriction frequent | Complete occlusion of a coronary vessel<br>Complete ischemia<br>No reflex mechanism |
| Pathology | Coronary artery involvement variable—vessels normal to severely diseased; usually sclerotic<br>No acute muscle changes in simple episode of angina pectoris<br>In severe form diffuse, disseminated focal areas of necrosis in subendocardium and papillary muscles<br>No, or little involvement of the pericardium or endocardium and hence no pericarditis or mural thrombosis with embolization | Coronary arteries invariably diseased<br>Infarction—massive, confluent extending from endocardium to pericardium<br>Pericarditis and frequent mural thrombosis with embolization |
| Predisposing | Arteriosclerotic, hypertensive, valvular and luetic heart disease | Arteriosclerotic and hypertensive heart disease |
| Exciting | Effort, emotion, extremes of heat and cold, food, tobacco plus liquor, valvular heart disease, anesthesia, operation, shock, heart failure, tachycardia, auricular flutter or fibrillation, fluctuations in blood pressure, hypoglycemia, adrenalin, anoxemia, carbon monoxide poisoning, hemorrhage, anemia, pulmonary infarction and embolism, status asthmaticus, visceral reflexes, sexual intercourse, straining at stool, infection, trauma, hyper- and hypothyroidism | None<br>Possibly operation, shock or drop in blood pressure? |
| Laboratory Findings | None in simple attack of angina pectoris<br>If myocardial necrosis present, then fever, leukocytosis, rapid sedimentation rate—but usually not very marked | Fever, leukocytosis, rapid sedimentation rate |
| Fever | None or slight | Constant, 100° to 103°F. usually |
| Pain | Slight to severe<br>Usually relieved by nitroglycerin | Usually severe<br>Not relieved by nitroglycerin, in fact condition aggravated |
| Gastrointestinal | Nausea and vomiting not present in simple attack of angina pectoris | Nausea and vomiting common |
| Cardiovascular: | | |
| Shock | Usually absent | Common |
| Heart Sounds | Usually no change | Poor, tic-tac, embryocarditic, gallop |
| Pericardial Rub | Absent | Present |
| Blood Pressure | Usually no change; may rise during pain | Definite fall |
| Tachycardia and arrhythmias | Usually absent except as a precipitating agent | Common after the onset |
| Heart Failure | Variable | Common; lungs often congested |

TABLE II* (*Continued*)

| | Acute Coronary Insufficiency | Acute Coronary Occlusion |
|---|---|---|
| Electrocardiogram | RS-T depressions<br>T wave inversions | RS-T elevations into T wave inversions<br>Large Q-waves<br>Reciprocal relationship between leads I and III |
| Treatment | Preventive and curative<br>Avoid cause and treat exciting factor; transfusion for hemorrhage, digitalis for heart failure, etc. | No specific treatment except for complications |
| Duration of Illness | Seconds, minutes, hours and days | Weeks, months and years |
| Condition after Attack | Good in angina pectoris; variable otherwise | Poor |
| Degree of Recovery | Complete for single attack of angina pectoris; variable otherwise | Prolonged illness and earmarks of attack for years |
| Prognosis | Variable; depends on precipitating factor | Fatal outcome not uncommon; signs and symptoms usually permanent |
| Compensation | Compensable | Not directly compensable |

* Slightly modified from *New York Medicine* 2: 9, 1946.

examination of the hearts revealed that the proportion of deaths due to acute coronary artery diseases was 49.5 per cent, and for the year 1938 was actually 54 per cent. (Table I.) It is obvious, then, that coronary diseases are by far the most important of all heart diseases.

With the lengthening span of life, and an increasing older population, the number of victims of coronary disease will continue to increase. According to the National Resources Planning Board[47] there were in this country in 1900, 8,500,000 persons between the ages of fifty and seventy-four years; in 1940, 24,000,000, and in 1980 there will be 42,000,000. Since two thirds of the episodes of acute coronary diseases occur in this older age group it is apparent that the number of cases will be even greater than it is today.

## DIFFERENTIATION OF ACUTE CORONARY DISEASES

There are two main divisions of the acute coronary diseases: (1) acute coronary occlusion, and (2) "acute coronary insufficiency" (without acute occlusion.)

*Acute coronary occlusion*, (Table II) is the term used to indicate sudden complete closure of the coronary artery, a sequel of progressive arteriosclerosis. The attack occurs fortuitously, at any time, anywhere, and is not related to effort and excitement. In fact, it takes place most frequently during sleep and rest, simply because the major part of the day is spent in these states. The symptoms and signs of crushing substernal pain (not relieved by nitroglycerine), nausea, vomiting, shock, fall in blood pressure, change in heart sounds, gallop rhythm, fever, leukocytosis and increased sedimentation rate, are well known. The illness is prolonged and usually results in permanent changes in the heart. At autopsy, the lumen of the coronary artery will be found completely closed by a thrombus formed directly on an arteriosclerotic plaque, or originating from an intimal hemorrhage breaking through the endothelial lining of the plaque. Occasionally a hematoma within an intimal plaque causes complete obstruction of the lumen without thrombosis. The infarct is large, usually extending from the endocardium to the pericardium. The resulting pericarditis may give rise to a friction rub. Involvement of the endocardium frequently results in mural thrombus forma-

tion and peripheral embolization. The electrocardiogram is specific. Elevations of the RS-T segments progress steadily to inverted T waves. Large Q waves and a reciprocal relationship between Leads I and III are present. The RS-T elevations are associated with the epicardial and subepicardial involvement, the Q waves with the massive through-and through injury to the ventricular wall, possibly septal damage.

In *acute coronary insufficiency* (*without acute occlusion*) (Table II) there are gradations of severity of the heart attacks. The simple short episode of angina pectoris, in which the chest pain is momentary, is brought on by exertion, excitement, ingestion of food, cold, and the like, and is relieved by nitroglycerine and rest. Gastrointestinal manifestations, fever, leukocytosis and increased sedimentation rate are not present. When the pain has disappeared, the patient's condition is good. The blood pressure does not fall; in fact, it may rise. Acute alterations in the myocardium do not occur. An electrocardiogram taken during an attack may show transient RS-T depressions and T wave inversions, or it may be normal.

In a more severe type of acute coronary insufficiency (without acute occlusion), the anoxia of the heart muscle is prolonged so that serious injury to the latter may take place. A synonymous term for this type of attack is acute myocardial necrosis without acute occlusion. The chest pain may be severe and moderately prolonged. The episode is often related to exertion, excitement and emotion. It may occur after sexual intercourse, straining at stool or following gastroenteritis. It may be induced by extremes of heat and cold, tachycardia, auricular fibrillation or auricular flutter, shock, heart failure, hypoglycemia, operation, anesthesia, anoxemia of many types, carbon monoxide poisoning, acute hemorrhage, chronic anemia, hyperthyroidism and hypothyroidism. It is a consequence of pulmonary infarction and embolization, of infection and trauma; it occurs reflexly from abnormal or diseased abdominal viscera. The symptoms and signs are those to be expected in a disease that is more serious than the simple syndrome of angina pectoris, but frequently they are not so grave as similar manifestations of acute coronary artery occlusion. Chest pain, shock, change in heart sounds, fall in blood pressure, fever, leukocytosis and increased sedimentation rate, if present, are usually not so marked as in acute coronary occlusion. In a severe episode, the heart muscle may contain many focal, or even diffuse, areas of subendocardial necrosis. These areas are often observed in the papillary muscles, but the endocardium and the pericardium are not involved. For this reason, thrombus formation on the heart wall with subsequent embolization is not encountered and pericardial rub is not heard. The electrocardiogram discloses depressions of the RS-T segments and T wave inversions in one or more leads. The localization of the myocardial necrosis to the subendocardium may be explained by the assumption that this region of the myocardium receives the poorest blood supply. Small branches from the coronary arteries turn at right angles into the cardiac muscles and beneath the endocardium. Hence, this area is farthest from the source of nourishment and suffers most when the coronary flow is diminished. The endocardium itself receives blood directly from the ventricular cavity.

The differences in the electrocardiograms in coronary insufficiency and coronary occlusion can be explained by the dissimilar pathologic changes. It has been suggested[56, 65, 66] that the elevation of the RS-T segment in coronary occlusion is associated with the pericardial involvement common in this condition. In coronary insufficiency, the areas of necrosis are focal and scattered and chiefly subendocardial; the pericardium is spared. Therefore, depression of the RS-T interval replaces elevation of this segment.

Recently Boyd and Scherf[58] showed that injury to the epicardium at the apex of the heart produces a high take-off of the RS-T segment, whereas injury to the endocardium produces depression of this segment with slight inversion of the T waves.

The prognosis of acute coronary insufficiency without acute occlusion, even when myocardial necrosis is present, is usually better than that of acute coronary occlusion with infarction.

Treatment of these two types of acute coronary diseases differs. A rational existence, mentally and physically, a change in climate, avoidance or elimination of known precipitating causes such as unusual or severe effort, trauma, overexcitement, extremes of heat and cold, overeating, excessive smoking together with drinking, will prevent acute coronary insufficiency without acute occlusion. During operation or anesthesia an adequate supply of oxygen must be administered in order to avoid cyanosis. Adequate treatment, or better, prevention of shock is indicated. Administration of digitalis and the mercurial diuretics in heart failure, digitalis and quinidine for tachycardia, auricular fibrillation and flutter, blood transfusions for hemorrhage or anemia, avoidance of reflexes from the abdominal viscera, prevention or cure of infection perhaps by means of the sulfonamide drugs, penicillin and streptomycin, are all measures of value in preventing acute damage to the heart muscle. In acute coronary occlusion, on the contrary, avoidance of these predisposing factors will not prevent the onset of acute coronary occlusion. The best treatment for this is passive; active or drastic measures should not be employed unless complications make it necessary to intervene.

## CONFUSION OF TERMS AND THOUGHT

It would be well to point out the existing confusion in the terminology employed in coronary artery diseases.[48] A number of expressions in use, including angina pectoris, coronary occlusion and coronary thrombosis, coronary insufficiency, coronary failure and myocardial infarction, are often applied loosely and given various connotations.

The distinction between acute coronary insufficiency and acute occlusion is confused by careless use of terms. The term, acute coronary occlusion should be applied only to sudden complete obstruction of a vessel. The clinical syndrome and the electrocardiographic findings are characteristic and the diagnosis is readily made. The adjective "acute" should be employed in order to distinguish the sudden catastrophic episode from chronic progressive arteriosclerosis of a coronary artery resulting in partial or practically complete obstruction of the lumen. Blumgart and Schlesinger,[49] in their otherwise excellent investigation, used the term coronary occlusion to indicate arteriosclerotic narrowing whether or not there was acute complete occlusion.

The expression "acute coronary insufficiency" should be employed in the restricted sense which we have used. It should not be employed to include all of the acute coronary diseases as is so frequently done. Of course, the qualifying phrases "with acute occlusion" or "without acute occlusion" would be descriptive and most accurate, but experience has shown that few have adopted them.

The term "myocardial infarction" is sometimes used without qualification, an unfortunate circumstance, since the meaning of this term is too broad to permit of its being an exact diagnosis. When "myocardial infarction" is employed, its meaning should be delimited by adding either "with acute coronary occlusion" or "without acute coronary occlusion."

In addition to recognition of the clinical variations in the several coronary artery diseases and to properly defined terminology, correct diagnosis will be further assured if electrocardiographic changes are properly

interpreted. The presence of RS-T elevations alone are characteristic of pericarditis[50] but not of acute coronary occlusion.[51] RS-T depressions which appear alone are typical of involvement of the inner or subendocardial region of the heart[36, 52, 53] and should not be interpreted (which frequently happens[54, 56]) as indicative of acute coronary occlusion. Many investigators have shown that damage to the inner surface of the heart results in RS-T depressions, whereas epicardial injury is associated with RS-T elevations.[50]

The clinical and electrocardiographic characteristics of the various acute coronary diseases have now been so extensively verified by postmortem examination that with proper appreciation of these characteristics, diagnosis in any given case can be made with assurance. The classical clinical signs and electrocardiographic pattern of acute coronary occlusion will be corroborated at autopsy in 95 per cent of the cases.[40, 57]

## INCIDENCE OF ACUTE CORONARY OCCLUSION

The incidence of acute coronary occlusion is not readily obtainable. The census includes acute coronary occlusion under diseases of the coronary arteries and angina pectoris. An estimation of the actual number of deaths from acute coronary occlusion was made by sampling New York State death certificates and applying the figures thus derived to the rest of the country. It was computed[58, 59] that at least 25 per cent of deaths reported under "diseases of the myocardium," 60 per cent of those ascribed to "coronary disease" and 80 per cent of those listed as "angina pectoris" were, in fact, instances of acute coronary occlusion. On the basis of these percentages, it was calculated that there were 120,000 deaths from acute coronary occlusion in this country in 1942. If the mortality rate for this disease is accepted as 15 per cent, there are about 800,000 attacks of acute coronary occlusion yearly.

Using the United States census figures[58] for the number of men and women in this country over forty years of age, and a coronary disease incidence ratio of 3 men to 1 woman, we may conclude that approximately 1 man in 40 and 1 woman in 115 experiences an attack of acute coronary occlusion yearly. These figures will, of course, vary if other mortality rates are adopted for the computation. There is evidence[59] that the number of instances of acute coronary occlusion may be as high as 1,000,000; if this figure is accepted, 1 man in 30 and 1 woman in 90, forty years of age and over, annually sustain acute complete obstruction of a coronary artery.

## INCIDENCE OF "ACUTE CORONARY INSUFFICIENCY"

It is my opinion that the incidence of acute coronary insufficiency (without acute occlusion) is of the same magnitude and significance as is that of acute coronary occlusion. Although further and extensive tabulation of the comparative incidence of these two types of coronary artery disease is needed, certain figures to be found in recent reports are significant. Kroetz[60] believes that acute coronary occlusion and acute coronary insufficiency without acute occlusion occur with equal frequency. He found acute occlusion in 55 per cent of his cases and acute coronary insufficiency without occlusion in 45 per cent.

Levy and Bruenn[61] in a review of the postmortem examinations of 376 cases in which death was due to coronary sclerosis, found only thirty-nine instances of coronary thrombosis. This is, of course, an unusually low percentage, and the authors themselves point out that a close examination of the coronary arteries would undoubtedly have brought to light many more instances of acute occlusion.

French and Dock[62] describe eighty deaths from acute coronary artery disease which occurred among young soldiers. Only twenty-nine or 36 per cent of the deaths were cases of acute coronary occlusion, and I believe the majority of these actually represented acute coronary insufficiency without acute occlusion.

A review of the autopsies at the Mount Sinai Hospital, New York, for the five years 1941–1945 inclusive, reveals that about 70 per cent of deaths from acute coronary disease were due to acute occlusion; in the remaining 30 per cent acute occlusion did not occur. These figures are merely approximate, and in the near future we hope to obtain accurate ratios.

Although the foregoing statistics obviously do not furnish adequate evidence on which to base conclusions, they do indicate that deaths from acute coronary insufficiency are perhaps as common as deaths from acute coronary occlusion. The medical examiners of the City of New York and Newark, New Jersey, are of the opinion that in sudden unexpected deaths, acute coronary insufficiency is observed even more frequently than is acute complete obstruction.[63] Moreover, it should be kept in mind that the non-fatal cases of acute coronary insufficiency far outnumber the non-fatal cases of acute coronary occlusion. Simple episodes of angina pectoris fall in the former category. Even a severe form of the disease, accompanied by myocardial necrosis, culminates in death far less frequently than does acute coronary occlusion.[38]

## CORONARY DISEASE AND INDUSTRY

It is appreciated today as never before that industry has a special interest in acute coronary artery diseases. In June, 1946, nearly 57,000,000 persons were employed in this country.[64] In New York State alone $61,000,000 is paid out yearly[65] in claims arising from employment; and in the United States as a whole, compensation claims for the year 1943 amounted to $360,000,000.

Coronary artery disease plays no minor rôle in the field of compensation insurance. Indeed, the chronological relationship between work and an acute coronary episode is so dramatic that it is often assumed that every type of acute coronary disease is precipitated by exertion, excitement or trauma. This assumption is true as far as attacks of acute coronary insufficiency without acute occlusion are concerned. It is so evident that it may be accepted as a matter of fact. Existing controversy is concerned with the causation of acute coronary occlusion. As I have already stated, this condition is, in my opinion, an end result of long standing sclerosis of the coronary arteries and its onset cannot be attributed to any factor in the external environment, with the possible exception of shock and fall in blood pressure.

There would be less discussion and more agreement concerning the precipitating factors of acute coronary disease were it generally realized that there are two main acute coronary artery diseases, each distinct clinically and electrocardiographically from the other, but both due to a common underlying anatomical predisposing condition, namely, arterisoclerosis. Because exertion, excitement or trauma can cause acute coronary insufficiency,[66] this disease is definitely compensable among workers. Acute coronary occlusion, however, is a sequel of arteriosclerosis and is not precipitated by effort or excitement,[2] and therefore is not compensable.

The part played by effort, occupation and trauma in precipitation of acute coronary artery occlusion will be discussed in turn.

*Rôle of Effort in Acute Coronary Occlusion.* First, let us consider effort as a precipitating factor. My colleagues and I determined the events associated with the onset of 1,068 attacks of acute coronary occlusion by obtaining a detailed history of the activities

of the patient immediately prior to the attack and during the preceding hours, days and weeks.[2] The results are given in Table III. Fifty-two per cent of the attacks occurred

TABLE III
TYPES OF ACTIVITY AT ONSET OF CORONARY OCCLUSION (1,068 ATTACKS)

| | PER CENT |
|---|---|
| Sleep | 22.5 |
| Rest | 29.5 |
| Ordinary mild activity | 21.0 |
| Moderate activity (except walking) | 9.0 |
| Walking | 16.0 |
| Unusual or severe exertion | 2.0 |
| Total | 100.0 |

while the patient was asleep or resting; 21 per cent, during mild routine activity; 16 per cent, while walking; and 9 per cent, during moderate activity, such as pressing, painting and baking. In only 2 per cent of the cases was a history of unusual physical exertion obtained. Since these activities were engaged in by the patients for the portions of the day ordinarily spent in such pursuit, they must be ruled out as factors in the onset of occlusion. For example, almost half of the day is usually occupied in sleep or rest, and therefore the occurrence of half of the attacks during these states must be considered coincidental. The same inference may be drawn from the percentage for mild and moderate activity, as well as from the figure for unusual exertion, which preceded the attack in only 2 per cent of the cases. Even when a person guards against undue exertion some action requiring severe effort is usually performed during the day. Consequently, if effort were a factor in precipitating coronary occlusion the two would be associated much more frequently than they are and occlusion would be much more common than it is. In this connection it is worth noting that because of chronic illness, such as heart failure, cancer and surgical complications, at least seventy-five of the patients had been confined to bed for considerable periods prior to the occurrence of the occlusion.

*Rôle of Occupation in Acute Coronary Occlusion.* There have been conflicting reports concerning the relation of occupation to coronary occlusion. Some authors believe that coronary occlusion occurs most commonly among the laboring classes, whereas others have stated that it is more frequently observed among persons engaged in sedentary occupations and among business and professional people.

In a series of 1,268 cases in which we studied this factor, coronary occlusion occurred with equal frequency in all occupational groups.[67] In order to compare our occupational distribution with that of the general population as given by the U.S. Census, we divided our cases into three groups: workers and laborers, store, office and business men, and professional persons. We found that the ratios were almost identical with those for the general population of New York City. For instance, the first group comprised 51 per cent of our series and 55 per cent of the population; in the second group, the figure was 37 per cent, for both; the third group was 12 per cent in our series and 8 per cent of the population. Such close correspondence between the percentages eliminates occupation as a predisposing factor in coronary occlusion. Were coronary occlusion precipitated by effort, the incidence of strenuous occupations should be greater than that obtained in our series. Actually the percentage of sedentary persons was the same as that of heavy laborers.

*Rôle of Trauma in Acute Coronary Occlusion.* Attempts have been made to prove a causal relationship between trauma and coronary occlusion, but examination[68] of the published report on the subject reveals that many of the cases cited as trauma were caused by contusion of the heart and not by coronary occlusion. Indeed, in most instances the authors failed to differentiate the two conditions. In some of the cases reported postmortem examination was not made; the

presence of coronary occlusion was simply assumed despite the fact that the clinical similarity of the two conditions is marked. In certain other acute cases in which coronary occlusion was known to be present, not only had a long interval elapsed between the occurrence of the trauma and death, but there was pre-existing severe acute coronary artery disease, two facts that would suggest that the occlusion was not related to the trauma. From our study of reported cases and from our own experience we have been led to conclude that available evidence does not support the theory of causal relationship between trauma and classical acute coronary occlusion. On the other hand, trauma, direct and indirect, to the chest and even to the abdomen can produce arrhythmias and damage to the heart. It is, of course, conceivable that a severe injury could contuse a coronary artery with resulting closure of the lumen and infarction of the ventricle wall. However, an accident of this type would happen very rarely.

The rôle played by trauma in the initiation of coronary occlusion requires much more careful and critical investigation than it has received. Too often doubtful cases in the literature have been accepted as proved and cited as such by subsequent writers. The effect on the heart of trauma produced for experimental purposes is sometimes cited as proof of association of injury and acute coronary occlusion despite the fact that in such experiments contusion of the heart, not acute coronary occlusion, is produced.

*Outlook for Patients Following Recovery from Acute Coronary Occlusion.* The question as to whether or not patients should return to work following an attack of acute coronary occlusion is of practical importance both medically and economically. If he may return, how soon is it permissible to do so? Is it true, as some physicians believe, that return to work leads to further acute coronary occlusion and heart failure? These questions are also significant from the standpoint of compensation insurance. Many persons possess disability policies and it has been assumed that acute coronary occlusion always indicates permanent and total disability. Positive answers to these questions cannot be given in the present state of our knowledge, but for many years I have urged that a more hopeful outlook should be adopted than that usually taken. Eleven years ago I found that fifty-three of seventy-five private patients had resumed their original work after recovery from an occlusion; only 8 per cent were completely disabled.[69]

Detailed follow-up data on 422 private and ward patients who had recovered from an attack of acute coronary occlusion is now available.[67] These patients came from all strata of society and were observed for intervals varying from six months to fifteen years, the average period being three and one-half years. Twenty per cent were followed five years or more. The ratio of men to women was 4½ to 1. Almost 90 per cent were in the age group forty to sixty-nine years, the sixth decade predominating. Three-quarters of the patients were seen in their initial attack, and almost all the others in their second.

Fifty-three per cent of the patients returned to work after recovery from the attack, 92 per cent of these doing so within one year. Actually, one-half resumed their occupations within three months after discharge from the hospital and three-quarters did so within six months. In the majority of cases, the work was full-time. The percentage of those returning to work was greater among the private patients than among the ward patients. Sex did not play a rôle in this respect.

There was a close correlation between resumption of work and age; the younger the patient, the more likely he is to return to work. In our series, 73 per cent of those in

the fourth decade resumed work, whereas only 43 per cent of those in the seventh decade did so.

Presence of previous attacks had a significant influence on rehabilitation following coronary occlusion. Fifty-nine per cent of the patients suffering a first attack resumed work; whereas only 38 per cent of the patients who had a second attack, and 23 per cent of those who had a third attack did so. Each successive attack reduces the probability of return to work; although one patient was able to work again following a fourth attack.

In our series only half the laborers resumed their occupations; two-thirds of the white-collar and office workers and four-fifths of the professional persons returned to work. The majority of those engaged in professions were able to work full time, whereas half of those in other occupations worked only part time. This difference in ability to resume work is more apparent than real since persons engaged in professional and executive pursuits can do relatively light work even on a full-time basis. In addition, they usually have a greater incentive to take up their occupations again.

As was to be expected, many of the patients who returned to work complained of such symptoms as weakness, precordial pain and dyspnea. This was true of about half the group, particularly the laborers, white-collar workers and housewives. However, their symptoms were not severe enough to preclude work; indeed, in many of these patients similar symptoms were present before the attack.

A considerable group ceased to work on the advice of their physicians or because they possessed disability insurance; some patients naturally were unable to find positions. We believe that a considerable proportion of this group would have resumed work had it been necessary. It is probable that in our entire series well over 60 per cent of the patients recovered sufficiently to take up their customary occupations again had they wished to do so.

Evidence gathered from observation of 1,068 attacks of coronary occlusion indicates that the onset of an attack is not related to external factors such as effort, work or trauma; nor is it confined to any particular occupation or social strata. Coronary occlusion is the end result of a progressive atherosclerotic process and occurs as often in the sedentary individual as in one engaged in active work.

Our findings also indicate that an attack of acute coronary occlusion without complications is not in itself a reason for permanent or total disability. We believe that the outlook for a patient following recovery from an attack of coronary occlusion may justifiably be regarded more hopeful than in the past.

## COMMENT

With the exception of isolated instances in which differentiation may be difficult, acute coronary insufficiency and acute coronary occlusion can be diagnosed as readily as can acute appendicitis. In the latter disease, diagnosis may occasionally prove troublesome. Thorough understanding of the clinical and electrocardiographic characteristics of the coronary diseases will enable the clinician to specify the type of acute coronary diseases present in almost every case. Naturally the clinical picture of the two types of acute coronary insufficiency will overlap at times. Occasionally, acute coronary insufficiency will cause acute myomalacia which is confluent and extends through from endocardium to pericardium, simulating acute coronary occlusion. This condition may arise when sclerosis of the coronaries is very severe and long standing.

Some writers[49,70] have been prompted to discard the term coronary occlusion on the assumption that it is impossible clinically to differentiate acute coronary occlusion with

infarction from acute coronary insufficiency with focal necrosis or infarction, but without acute occlusion. They consider that the term coronary occlusion should be confined to postmortem reports. I do not agree with this point of view, for, in my experience, acute coronary occlusion presents characteristic clinical and electrocardiographic changes which are almost always distinguishable from those produced by infarction caused by acute coronary insufficiency in which acute occlusion is not present.[38]

Acute coronary occlusion is to my mind a valuable diagnostic term. Not only does it embrace a typical syndrome, well known to every physician, but it is associated with a characteristic, progressive electrocardiographic pattern. The fact that in some cases acute coronary occlusion does not produce characteristic electrocardiographic changes, should not militate against the use of the term. In most cases of this type the electrocardiogram had been previously abnormal as a result of old coronary occlusion, bundle branch block, or marked enlargement of the heart, and the advent of another acute occlusion or of myocardial necrosis without acute occlusion may not alter the electrocardiogram significantly, or may produce equivocal or non-specific changes. In such cases the presence of a precipitating factor, such as effort, emotion, shock, operation or hemorrhage, should suggest acute coronary insufficiency without acute occlusion. The diagnosis can be made if the clinical picture of this condition is present, i.e., the pain not infrequently is mild, pericardial rub is absent and heart failure usually is not severe. Fever, leukocytosis and rapid sedimentation time are, as a rule, less marked than in acute coronary occlusion.

The concept of angina pectoris has undergone considerable change in recent years. It is now generally agreed that the attack represents temporary insufficiency of the coronary flow, and it has been suggested, therefore, that the term angina pectoris be discarded, and another, such as transitory acute coronary insufficiency, be employed. Theoretically this change would be justified. However, the classical syndrome of angina pectoris, including the typical substernal pain and its radiation, its relation to effort, excitement, cold, and eating, and its relief by rest and nitroglycerin, is so characteristic and firmly established that it would seem advantageous to retain the term to connote acute coronary insufficiency without myocardial involvement.

## SUMMARY

Acute coronary artery diseases have existed for hundreds, probably thousands of years. The arteriosclerosis observed in Egyptian mummies was of the same nature as is this disease today. Descriptions in the Bible are suggestive of attacks of acute coronary occlusion. Hippocrates is quoted as saying that "Cardiodynia, which occurs more frequently in senility, foretells sudden death." However, present knowledge of acute coronary occlusion became established only after the reports by Herrick in 1912 and 1918.

Heart disease has, since 1912, been the chief cause of death in this country. Four to eight million people suffer from heart diseases. Coronary disease comprises from 25 to 50 per cent of all heart diseases. With the lengthening span of life and therefore an increasing older population, the number of victims will continue to increase in the future.

There are two main divisions of acute coronary artery diseases: (1) Acute coronary occlusion, and (2) acute coronary insufficiency (myocardial necrosis or myomalacia or myocardial infarction without acute coronary occlusion).

Acute coronary occlusion denotes sudden complete closure, a sequel of progressive arteriosclerosis. The attack is not related to effort and excitement. It takes place during sleep and rest and routine

activities of the individual. The symptoms and signs are crushing substernal pain, not relieved by nitroglycerin, nausea and vomiting, shock, fall in blood pressure, change in heart sounds, gallop rhythm, fever, leukocytosis and increased sedimentation rate. The illness is prolonged and usually results in permanent changes in the heart. At autopsy the lumen of the coronary artery is found completely closed. The infarct is large, usually extending from endocardium to pericardium. The electrocardiogram is specific.

In acute coronary insufficiency (without acute occlusion) the severity of the disturbance varies from the simple short episode of angina pectoris, in which the pain is momentary, to the more severe type in which the anoxia of the heart muscle is prolonged, so that a serious injury to the heart muscle may take place. The episode is often related to exertion, excitement and emotion; it may occur after sexual intercourse, straining at stool or following gastroenteritis; it may be induced by extremes of heat and cold, tachycardia, auricular fibrillation, auricular flutter, shock, heart failure, hypoglycemia, operation, anesthesia, anoxemia of any type, carbon monoxide poisoning, acute hemorrhage, chronic anemia, hyperthyroidism, hypothyroidism, etc. In a severe episode the heart muscle may contain many focal disseminated areas of subendocardial necrosis. These are often observed in the papillary muscles, but the endocardium and pericardium are not involved. The electrocardiogram discloses depression of the RS-T segments and T wave inversions which are characteristic. The prognosis of acute coronary insufficiency without acute occlusion is usually better than that of acute coronary occlusion with infarction. The former disease is compensable, the latter is not.

The treatment of these two types of acute coronary diseases differs. A rational existence and avoidance of the known precipitating causes prevent acute coronary insufficiency. Administration of digitalis, diuretics, quinidine, blood transfusions, etc., are of value in preventing acute changes in the heart muscle. In acute coronary occlusion, on the contrary, avoidance of predisposing factors does not prevent the onset of the attack. The best treatment of this is passive. Direct measures should be employed only if there are complications.

The distinction between acute coronary insufficiency and acute coronary occlusion is confused by careless use of terms. If the expression "myocardial infarction" is used as a diagnosis the qualifying phrases "with acute occlusion" or "without acute occlusion" are essential to accurate terminology.

There is evidence that the number of instances of acute coronary occlusion may be as high as 1,000,000 attacks per year. This means that one man in thirty and one woman in ninety, forty years of age and over, in this country annually sustain an acute obstruction of a coronary artery.

The incidence of acute coronary insufficiency is of the same magnitude and significance as that of acute coronary occlusion. In fact, in case of acute, sudden, unexpected death, acute coronary insufficiency is observed more frequently than is the acute complete obstruction.

Coronary disease is of great importance to industry. Nearly 60,000,000 people are employed in this country. Hundreds of millions of dollars are paid out yearly in compensation disability benefits.

Trauma, direct and indirect, can produce arrhythmias and damage to the heart. It very rarely if ever causes an acute coronary occlusion with infarction. In a severe steering wheel, or similar accident, with bruise of the chest wall and contusion of the wall of the left ventricle, an occlusion may rarely take place.

Evidence gathered from observations of

more than 1,000 attacks of acute coronary occlusion indicate that the onset of the attack is not related to external factors such as effort, work or trauma, nor is it confined to any particular occupation or social stratum. Acute coronary occlusion is the end result of an arteriosclerotic process and occurs as often in a sedentary person as in one engaged in active work.

Fifty-three per cent of patients return to work after recovery from the attack of acute coronary occlusion, nearly all of them within the first year. The younger the patient, the more likely is he to return to his employment. Each successive attack of acute coronary occlusion reduces the probability of return to work. Only half the laborers resumed their occupations, whereas two-thirds of the white collar and office workers, and four-fifths of the professional persons returned to their jobs.

Our findings thus indicate that an attack of acute coronary occlusion is not in itself a reason for permanent disability. We believe that the outlook for a patient recovering from an attack of acute coronary occlusion may justifiably be regarded more hopefully than it has been in the past.

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# Seminars on Rheumatic Fever

## Diagnostic Value of Roentgenography and Fluoroscopy in the Diagnosis of Rheumatic Heart Disease*

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ROENTGENOGRAPHY and fluoroscopy of the heart have been widely used for many years in the diagnosis of rheumatic heart disease. The method is valuable in conjunction with physical examination, electrocardiography and various laboratory procedures, but may be misleading if considered apart from the other procedures. My approach has at all times been that of the clinician trained in the use of this tool rather than that of the roentgenologist with a knowledge of heart disease.

The value of this method in rheumatic heart disease might be discussed under the following headings: (1) The value of roentgenology in arriving at an etiological diagnosis; (2) roentgenology in the estimation of anatomical sites of lesions; (3) the roentgenological manifestations of rheumatic activity; (4) roentgenology as an aid in estimating the age or duration of cardiac involvement; and (5) the clinical correlation between signs and symptoms and their roentgenological manifestations.

### VALUE OF ROENTGENOLOGY IN ARRIVING AT AN ETIOLOGICAL DIAGNOSIS

There are a number of conditions which at times may produce an image, particularly in the postero-anterior view, which simulates that seen so frequently in rheumatic cardiacs. A prominent pulmonic segment is not unusual in thyrocardiacs, and a straightening of the left upper cardiac contour occurs in chronic cor pulmonale, right heart failure secondary to left-sided failure, in congenital heart disease, and other disorders. Figure 1A shows a heart in the postero-anterior view triangular in shape, with a straightened left upper cardiac contour. The original report of the roentgenologist suggested "mitralization." This proved to be a case of chronic cor pulmonale secondary to bronchial asthma, emphysema and bronchiectasis. The right anterior oblique view (Fig. 1B) shows a bulge into the upper retrosternal space, while the course of the barium-filled esophagus indicates that the left auricle is not enlarged. The left anterior oblique view (Fig. 1C) shows a small left ventricle, a marked grade of inflow tract enlargement of the right ventricle, and enlargement of the right auricular appendix. It is obvious that the appearance in the postero-anterior view is not at all diagnostic; indeed the initial report was actually misleading.

There really is no typical roentgenological picture in rheumatic heart disease. In

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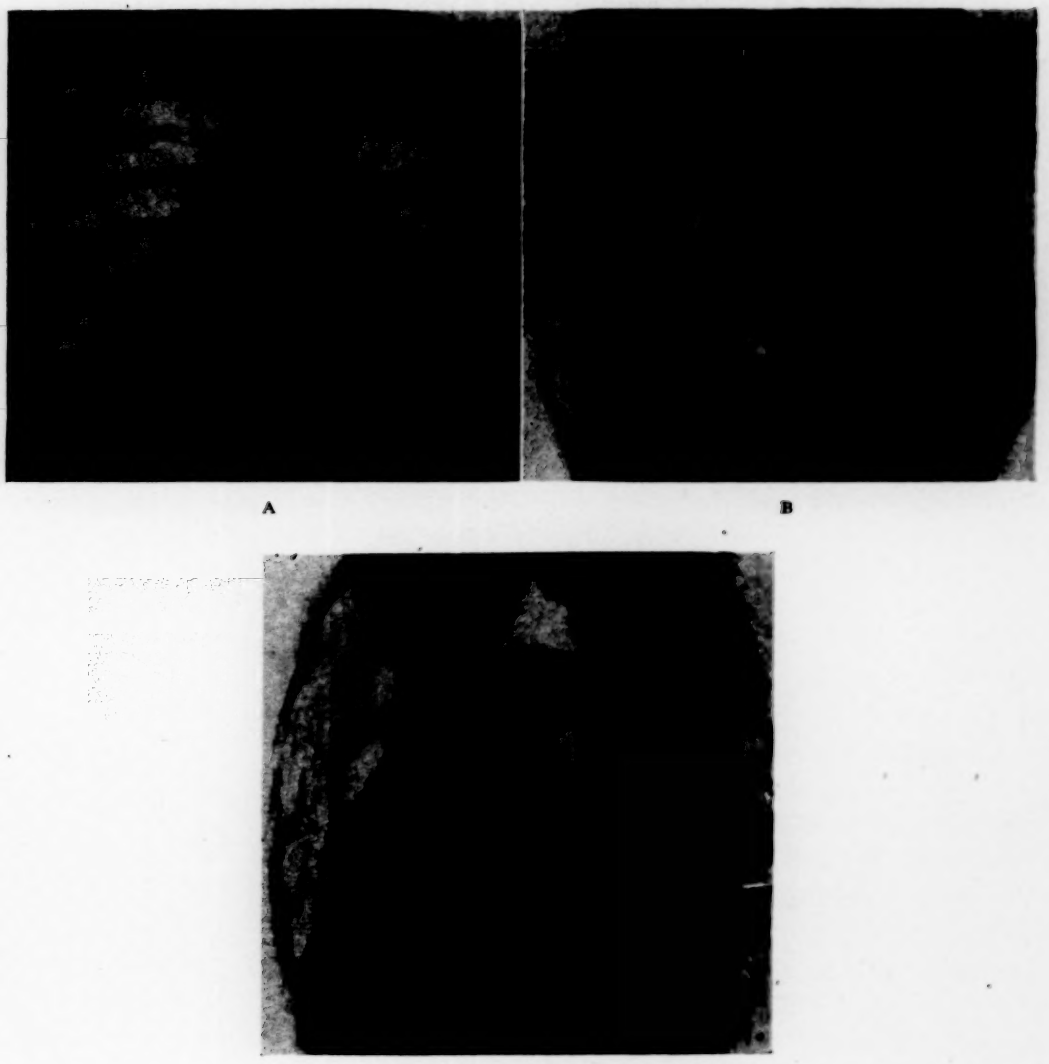


A B C

FIG. 1. A, B, C, roentgenographic illustrations from a case of chronic cor pulmonale.

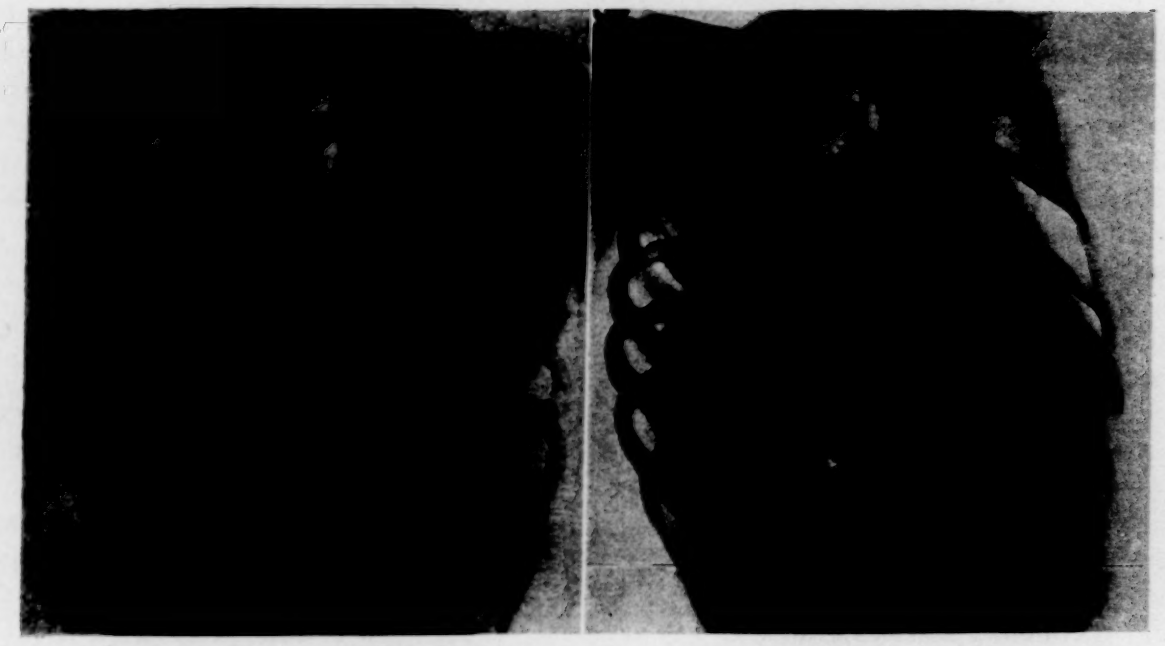
response to various kinds of damage there is cardiac chamber enlargement involving one, two or even all chambers. The frequently associated enlargement of the left auricle and the right ventricle occurs often in mitral valvular disease. However, it is the association of enlargement of the various individual chambers that is suggestive rather than the overall shape of the heart. A diagnosis of mitral valvular disease based on auscultatory findings is justified even in the absence of left auricular or right ventricular enlargement. Many such instances were found in examination of selectees for induction into the armed services.

### ROENTGENOLOGY IN THE ESTIMATION OF THE ANATOMICAL SITES OF LESIONS

Here recognition of individual chamber size is important. This is determined chiefly by fluoroscopy, while roentgenograms in the postero-anterior and in the right and left anterior and in the right and left anterior oblique positions are confirmatory, and give us a permanent record useful for comparison with subsequent examinations.

The left ventricle may be enlarged in

A



B C

FIG. 2. A, B and C, roentgenographic illustrations from a case of rheumatic heart disease with mitral stenosis and tricuspid incompetence. "X" marks the point of opposite pulsations.

mitral insufficiency and in aortic valvular disease. The grades of enlargement vary considerably. Aortic insufficiency may be associated with marked left ventricular enlargement, slight enlargement, or none at all. Mitral insufficiency on the other hand often causes no left ventricular enlargement, and when enlargement does occur it is usually slight or moderate in degree. In mitral stenosis the left ventricle is usually not demonstrably enlarged. Enlargement of the heart shadow to the left in such instances is due to the displacement of a small left ventricle to the left by right

ventricular enlargement. Figure 2A is the film of a young woman with mitral stenosis and tricuspid incompetence. Note the size of the left ventricle below the point of opposite pulsations marked "X." There is no elongation or rounding of this left ventricular segment, and in the left oblique view (Fig. 2B) there is no left ventricular bulge backwards or down. In the postero-anterior view (Fig. 2A) there is straightening of the left upper cardiac contour and a diminution in the size of the aortic knob. A double density is noted on the right due to an enlarged left auricle. In the left anterior oblique view (Fig. 2B) note, too, that the left auricle is large enough to have elevated and compressed the left main bronchus, that the inflow tract of the right ventricle is enlarged and that the right auricular appendix segment is elongated. The right anterior oblique view (Fig. 2C) demonstrates retrosternal bulge and left auricular enlargement.

To sum up: The left ventricle is not enlarged but is displaced to the left by right ventricular enlargement. The left auricle, the right ventricle and the right auricle are enlarged to a considerable degree. These findings served to corroborate the physical findings.

A boy with mitral valvular disease presented a long, loud, mitral systolic murmur but no diastolic murmur was heard. The left ventricular segment (Fig. 3A) below the point of opposite pulsation marked "X" is rounded and elongated. In the left anterior oblique view (Fig. 3B) the left ventricular segment is moderately enlarged. In this view, too, the left bronchus is elevated and compressed by an enlarged left auricle; the right auricle and inflow tract of the right ventricle are enlarged. The left auricle is greatly enlarged in the right oblique view (Fig. 3C), displacing a barium-filled esophagus posteriorly.

Finally, here is a third variant in left ventricular size, in a young man with rheumatic aortic insufficiency plus either mitral incompetency or mitral insufficiency. The left ventricle is greatly enlarged, the left auricle only slightly so, the other chambers are within normal limits, while the ascending aorta is elongated and dilated. The amplitude of left ventricular and aortic pulsations was increased, in conformity with the high pulse pressure and other Corrigan manifestations present in this case.

To sum up on the determination of anatomical sites of lesions: Various grades of chamber enlargement are associated with individual valvular lesions and with altered dynamic output.

It is possible to demonstrate calcified valves, especially when sought for actively, also calcification of the pericardium. Demonstration of systolic expansion of the left auricle indicates mitral insufficiency. Observation of expansile pulsations of the hilar arteries, termed "hilar dance," establishes pulmonary valvular insufficiency or incompetency.

## ROENTGENOLOGICAL MANIFESTATIONS OF RHEUMATIC ACTIVITY

The appearance and regression of a pericardial effusion in rheumatic cardiacs is generally acknowledged as evidence of rheumatic activity. It is also generally conceded that cardiac enlargement in rheumatic heart failure is due to active carditis. It is my belief that progressive cardiac enlargement, or the demonstration of individual cardiac chamber enlargement when compared with a previous examination even in the absence of congestive failure, is also an indication of rheumatic activity. This is true whether such enlargement is or is not associated with the usual manifestations of congestive heart failure. The chambers that are most frequently enlarged in rheumatic heart disease are the left auricle

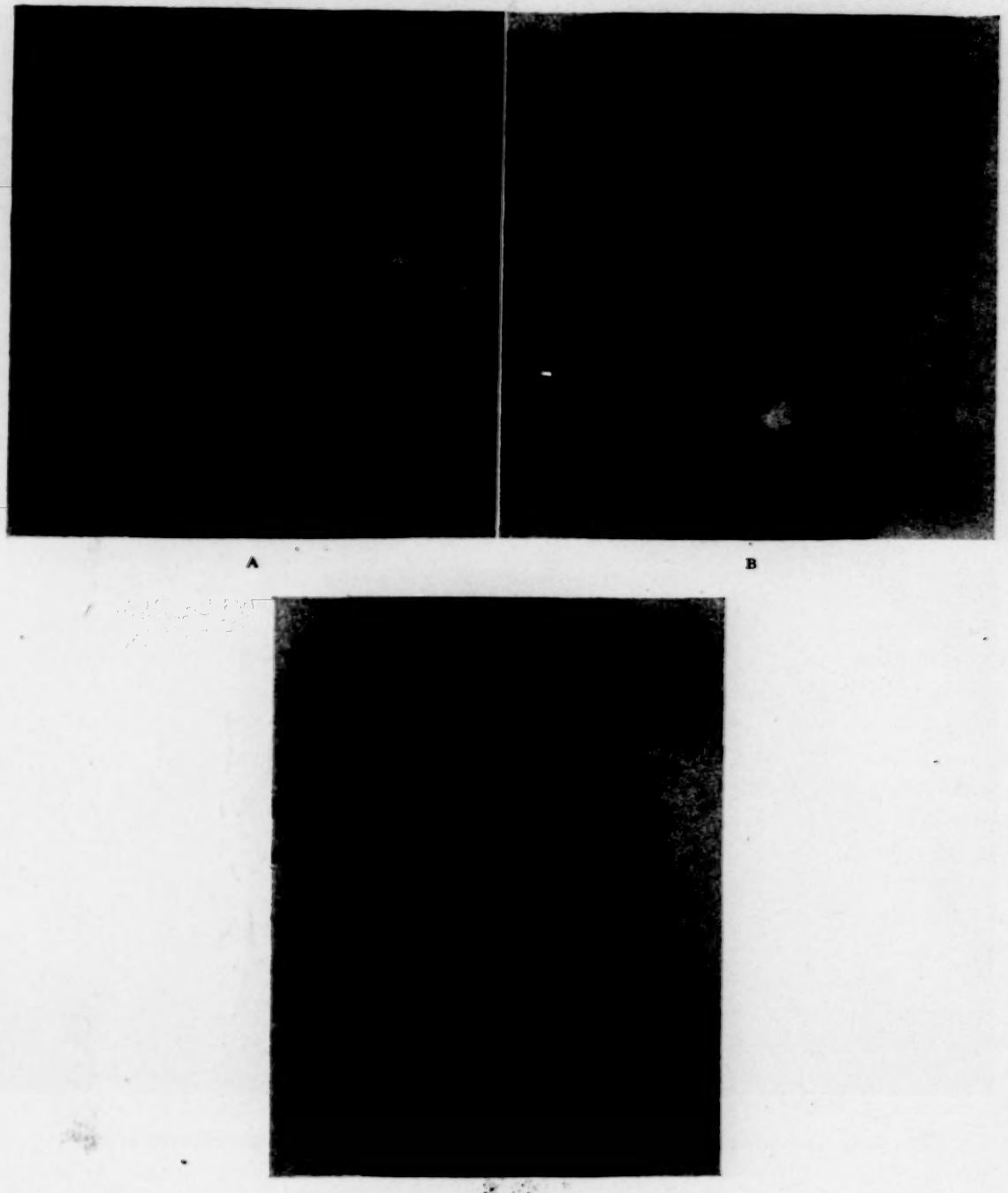



FIG. 3. A, B and C, roentgenographic illustrations of a case of rheumatic heart disease with mitral insufficiency. "X" marks the point of opposite pulsations as noted during fluoroscopy.

and the right-sided chambers, though not necessarily in equal degree. Here, however, was an instance in which the only manifestation of rheumatic activity, as far as I could determine, was in cardiac enlargement. Figure 4A is the film of a young woman with mitral stenosis. Fluoroscopy at this time showed a prominent conus segment in the postero-anterior as well as right anterior oblique views, no right ventricular inflow tract enlargement, but slight left auricular enlargement. She seemed perfectly well

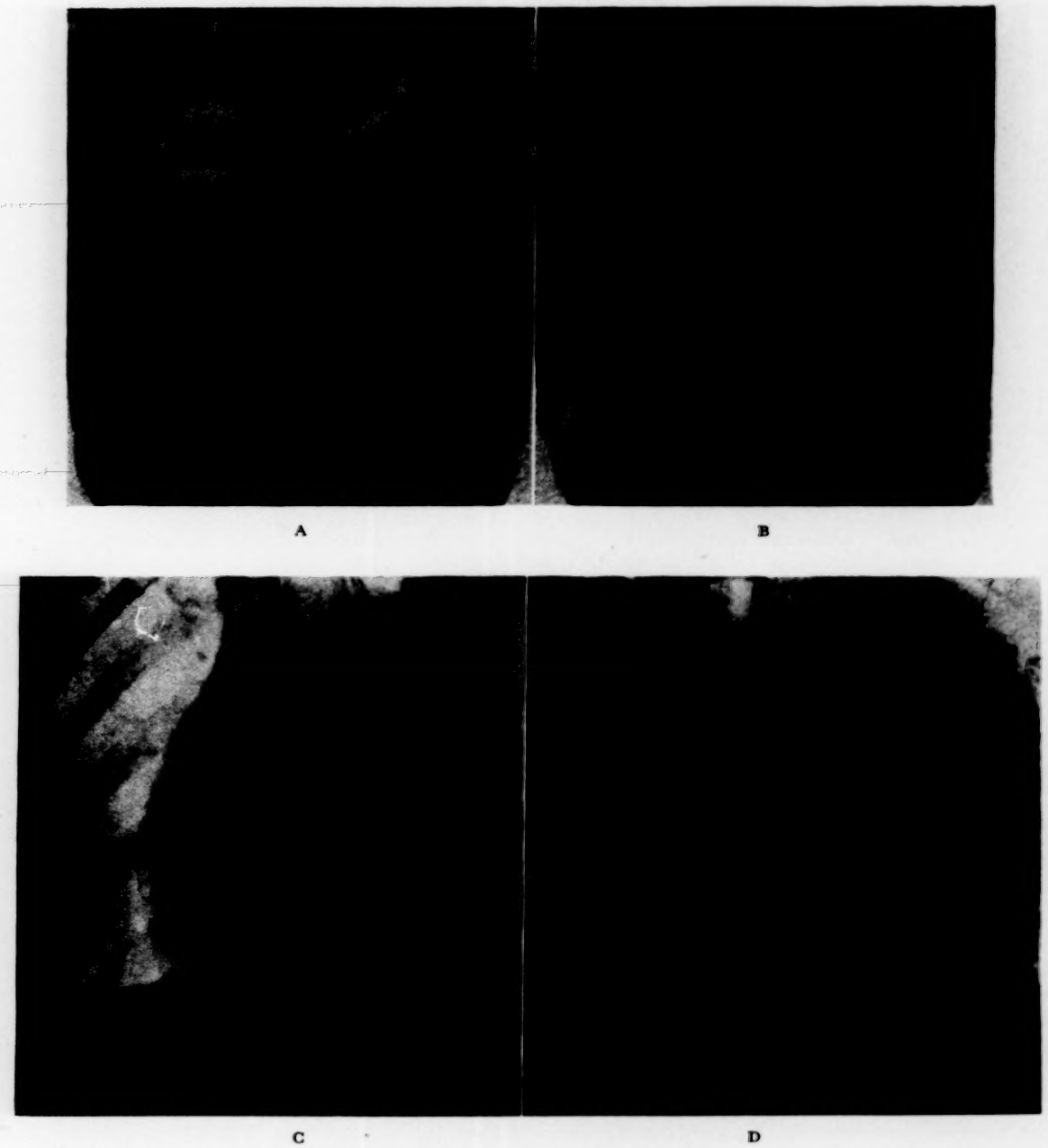


FIG. 4. A, B, C and D, cardiac enlargement as the only manifestation of rheumatic activity.

compensated, performed moderately strenuous duties without breathlessness or discomfort. Two years later (Fig. 4B) significant increase in cardiac size was noted. The left anterior oblique view (Fig. 4C) shows no significant right ventricular inflow tract enlargement, though a comparison film unfortunately is absent. The right oblique view (Fig. 4D) demonstrates moderate retrosternal bulge and slight left auricular enlargement.

At this point this girl was thoroughly rechecked. There was no change in her auscultatory findings. Her appetite and weight were unchanged. Her white blood count, differential count and sedimentation rate were within normal limits. Electrocardiograms failed to reveal any of the usual

criteria for rheumatic carditis. She had married and led an active social life including dancing and bicycling, in addition to her work.

On the basis of the roentgenological examinations, however, she must be regarded as having an active though smoldering type of rheumatic carditis. It might be argued that purely mechanical stress might have caused such enlargement. Against this are the numerous observations on other supposedly healed rheumatic cardiacs, subjected to similar physical stresses, who do not develop such cardiac enlargement. I therefore regard this patient, and others with similar cardiac chamber enlargements, even in the absence of the usual criteria for rheumatic carditis, as cases of rheumatic activity.

While on this point of rheumatic activity it might be well to mention that demonstrable calcification of a mitral or aortic valve, or calcified pericarditis, probably indicates cessation of rheumatic activity in at least the involved calcified areas. Other areas, however, may be the sites of active carditis in the same patient. (Fig. 5.)

FIG. 5. Calcified pericardium (see arrow) in a young woman with rheumatic heart disease, mitral, aortic and tricuspid valvular enlargement.

## ROENTGENOLOGY AS AN AID IN ESTIMATING THE AGE OR DURATION OF CARDIAC INVOLVEMENT

Valvular or pericardial calcification is a late manifestation in rheumatic heart disease. I have never found them before eight or ten years after the onset of the initial episode of rheumatic fever, this in spite of the fact that calcium deposition may occur within a matter of weeks or months. While on this point of calcification it might be well to discount the prevalent notion that calcified pericarditis is rarely rheumatic. It just isn't so. I know of four definite cases of calcified pericarditis in rheumatic cardiacs, three proven at autopsy, the other shown during life. (Fig. 5.)

Pulmonary fibrosis of the stippled variety, simulating miliary tuberculosis and at times also silicosis, is a late sequel of chronic recurrent pulmonary congestion in cases with rheumatic mitral valvular disease.

An interesting and an important aid in estimating the age of cardiac involvement is the finding of elevation and compression of the left main bronchus by an enlarged left auricle. Compression of the bronchus can occur only while the bronchial cartilage is soft and pliable, that is not beyond the teens. Elevation of the left bronchus without compression, however, may occur beyond that age. The finding of a compressed and elevated left main bronchus, therefore, indicates that left auricular enlargement occurred at or before the patient was fifteen, carditis often being unknown to the patient.

## CLINICAL CORRELATION BETWEEN SIGNS AND SYMPTOMS AND THEIR ROENTGENOLOGICAL MANIFESTATIONS

Patients with left ventricular enlargement, even of marked degree, may be completely or relatively asymptomatic. There have been athletes of considerable renown with aortic insufficiency and significant left ven-

tricular enlargement. Left auricular enlargement, due to mitral valvular disease or to mitral valvular incompetency with left ventricular enlargement, may be associated with pulmonary manifestations which vary considerably in degree. The occurrence of pulmonary congestion is usually accompanied by right ventricular enlargement. Enlargement of the right ventricular inflow tract and the right auricular appendix is usually associated with venous and hepatic engorgement, dependent edema, diminished blood flow to the pulmonary circulation, and in consequence there is a diminution in pulmonary congestion.

While on the point of correlation between signs and symptoms and roentgenological manifestations, it might be well to re-emphasize a point made previously, namely, that organic valvular disease may be present in the total absence of any cardiac chamber enlargement. I found hundreds of such instances while examining selectees for induction into the armed services, not only those with indubitable mitral valvular disease, but also many with aortic insufficiency. However, I recall no instance of aortic insufficiency with a high pulse pressure that was not associated with left ventricular enlargement.

The roentgenologic pulmonary manifestations of rheumatic disease may be classified as follows: (1) Pulmonary congestion, vascular and interstitial; (2) pleural effusions, general, loculated and interlobar; (3) pulmonary infarction; in cardiacs the latter is the most frequent cause of pulmonary densities, occurring more often than intercurrent pneumonic infections. Pulmonary infarction should be sought for not only when there are chest pains, fever and hemoptysis, but also when there are manifestations of collapse, pallor and cold sweats, or when the patient develops slight unexplained temperature elevations, or fails to respond to hitherto effective doses of digitalis or diuretics. The differential diagnosis here should always include rheumatic activity and pulmonary infarction. (4) Acute pulmonary edema: The central densities radiating from the hila, which have at times been described as the pulmonary manifestations of uremia, will frequently be found during or shortly after episodes of severe paroxysmal dyspnea and in pulmonary edema. Similar densities occur in paroxysmal pulmonary hemorrhages. (5) Chronic pulmonary edema, resulting in small, irregular, dense areas, usually in the lower portion of both lung fields; at times in larger densities, involving a complete lobe or more, due to localized failure to evacuate interstitial and alveolar fluid. The densities of chronic pulmonary edema must be differentiated also from atelectasis, plate-like areas of pulmonary infarction, interlobar effusions and pneumonitis. (6) Rheumatic pneumonia: large, small or confluent densities associated with active rheumatic carditis; (7) pulmonary fibrosis, and (8) pleural thickening.

In conclusion it may be said that roentgenology is of considerable assistance to us in rheumatic heart disease in various ways; as in the determination of heart chamber size, in evaluating associated pulmonary phenomena and complications, and in the recognition of various affections of the pericardium and valves. I might stress once again that it is only one of the methods, an important one, used in heart disease and as such must be correlated with other laboratory procedures and with the physical examination. Failure to appreciate the limitations of this method of examination may cause the examiner considerable grief and chagrin.

### DISCUSSION

DR. TARAN: Thank you, Dr. Schwedel. Your views fit in so well with some of the criteria for rheumatic activity that have

been evolved here at St. Francis Sanatorium. I am glad that Dr. Schwedel stressed that progressive cardiac enlargement is a manifestation of rheumatic activity rather than a result of mechanical stress caused by valvular defects. Are there any questions?

DR. ALLEN: Were the obliques taken with any sort of mechanical device to assure a proper angle of rotation?

DR. SCHWEDEL: No, these films were taken without any mechanical aids. I suppose a turntable or goniometer might be used once the degree of desired rotation has been established during fluoroscopy. There is no predetermined angle of rotation. The right auricular appendage is seen in its fullest extent in the earlier degrees of rotation into the left anterior oblique, and so is the ascending aorta. The left ventricle, however, may not be thrown clear of the spine, even in normal individuals until an angle of 60 to 65 degrees is attained. In the right oblique the optimum visualization of a retrosternal bulge as well as the retrocardiac projection of an enlarged left auricle will vary with each patient.

QUESTION: How do you differentiate between elevation and compression of the left main bronchus by an enlarged left auricle? Is there a definite pressure area?

DR. SCHWEDEL: In compression there is definite narrowing of the air-filled bronchus. Compression generally is associated with elevation of the bronchus, involving the entire bronchus, the central portion or the peripheral portion, or the elevation and compression may be arc-shaped.

QUESTION: Does the bronchial compression ever result in atelectasis?

DR. SCHWEDEL: I have never seen atelectasis attributable solely to bronchial compression. Bronchial narrowing, however, when associated with diaphragmatic elevation, pleural effusion or an intrabronchial mucous plug, may result in pulmonary alveolar collapse, a term preferable to atelectasis.

QUESTION: Are the miliary-like accumulations in mitral stenosis a manifestation of chronic passive congestion of the lungs?

DR. SCHWEDEL: No, these accumulations represent the residual end process of previous episodes of cardiac failure; areas of alveolar collapse and interstitial fibrosis resulting in localized millet-sized areas of fibrosis, simulating the picture in miliary tuberculosis, miliary carcinoma, sarcoidosis or early silicosis. In patients with such a picture a superimposed passive congestion will tend to obliterate the sharp outlines of these miliary-like densities. In chronic passive congestion the picture is one of diffuse haziness, plus increase in the width of the hilar arteries.

QUESTION: How often do you find a calcified valve?

DR. SCHWEDEL: Seek and ye shall find. Fifteen years ago a calcified valve had to hit me in the face before I recognized it. Since then I have found many, chiefly because I have trained myself to look for them. They are most frequently discovered during fluoroscopy, with shutters constricted to a relatively small opening. Small or larger areas of increased density, moving up and down or in a rotary motion with each cardiac cycle, indicate valvular or annular calcification. At times they are exceedingly difficult to register on films even with a spot film device.

Here is a film showing calcification of the mitral valve. In this right oblique view notice this vertical row of calcifications within the heart density.

Look at the barium-filled esophagus. Note the displacement due to left auricular enlargement. If you look closely, above there is displacement of the esophagus anteriorly in the region of the aortic arch; in the postero-anterior position the aortic compression is from the right, instead of from

the left as is normal. This type of esophageal displacement is caused by right aortic arch. The association of mitral stenosis and right aortic arch may be sheer coincidence but might be due to an interauricular septal defect. She had no demonstrable left ventricular enlargement, a large left auricle, and a marked degree of right ventricular and right auricular enlargement, dilated pulmonary arteries; all findings consistent with this diagnosis. She died but an autopsy was not obtained.

DR. WATTS: What is the source of emboli in pulmonary infarction in rheumatic fever cases?

DR. SCHWEDEL: The cause of pulmonary infarction usually is embolic, though I have seen instances of *in situ* thrombosis of pulmonary artery branches obliterating the lumen completely or partially, some of which resulted in pulmonary infarction. When the source is embolic it may come from a distal source, such as the calf veins, also pelvic and lumbar veins or the emboli may originate centrally from within the heart, more frequently when auricular fibrillation is present, but often enough when there is a regular sinus rhythm.

DR. RUBIN: If all of the criteria are absent in specific cases, except for progressive enlargement of the heart, how long is it before you say that activity has ceased?

DR. SCHWEDEL: If on repeated observations, say at six-month intervals, there is no further enlargement, the supposition is that this manifestation of rheumatic activity has ceased. Since it is rather difficult to evaluate slight changes in size a final decision on size should not be made in less than, say, two years.

There is a possibility that rheumatic activity may exist without clinical, laboratory or roentgenographic manifestations. The postmortem observations of Drs. Kugel, Rothschild and Gross in rheumatic cardiacs indicate that rheumatic activity was present in almost all below thirty, and in approximately a fifth beyond the age of fifty. While this group was not representative, consisting as it did of cardiacs in failure, it suggests that evidence for rheumatic activity is frequently unrecognized. It would be interesting to have more data gathered on rheumatic cardiacs who died of causes unrelated to their heart disease, groups of cases available to City Medical Examiners or to coroners.

DR. BENJAMIN: Do you believe that a patient with marked valvular involvement but without rheumatic activity will develop cardiac enlargement?

DR. SCHWEDEL: Such a patient may go on for years without enlargement. I suppose belief in enlargement on a mechanical basis need not be discarded entirely, but modified to the extent that if stress is unusual and prolonged, or complicated by such factors as hyperthyroidism or coronary artery disease or some other such factor which puts an additional burden on the original mechanical difficulties, then cardiac enlargement may occur.

DR. BENJAMIN: How about the cases with considerable valvular deformity, do they develop enlargement over a period of years?

DR. SCHWEDEL: Mechanically, no. I believe that unless complicated by other factors cardiac enlargement in rheumatic cardiacs should be considered as a manifestation of rheumatic activity.

DR. BENJAMIN: How about cardiac enlargement in congenital heart disease?

DR. SCHWEDEL: In congenital cardiacs, as well as other non-rheumatic cardiacs, enlargement is probably the result of a combination of mechanical causes plus such systemic factors as hypoxia, relative diminution in blood supply with one capillary serving an increase in muscle mass, plus complicating factors such as infection.

DR. DOWD: How does the heart compensate for a tight mitral valve without hypertrophy or enlargement?

DR. SCHWEDEL: I suppose you are referring to the instances of mitral valvular disease rejected for the armed services that I mentioned previously. Because of presystolic murmurs they were termed mitral stenosis. I seriously doubt whether they actually had real obstruction to the flow of blood into the left ventricle. We have all used the term mitral stenosis too loosely, and the term mitral valvulitis with deformity is preferable and correct. These cases had no left auricular or right ventricular enlargement. True cases of mitral stenosis with obstruction have left auricular and right ventricular enlargement.

The left auricle and right ventricle may be enlarged disproportionately. Dr. Benjamin Gouley, of Philadelphia, has pointed out that the right ventricle may enlarge even in the absence of left auricular enlargement, this being secondary to rheumatic involvement of the lungs.

DR. TARAN: Dr. Schwedel, would you expand a bit on the advantages and limitations of fluoroscopy in the study of rheumatic heart disease?

DR. SCHWEDEL: A fluoroscope is practical, convenient and is for most purposes accurate, at least I think it is so in my hands. For comparison purposes I have worked out a simple method for the estimation of transverse diameters which works out pretty well. By narrowing the shutters to a vertical slit I indicate the right and left outlines on the patient's chest or abdomen with a skin-marking pencil. This diameter, plus sketched fluoroscopic outlines in the postero–anterior and both oblique positions, are drawn in smaller scale on the chart, and the degree of enlargement of each chamber and the aorta is indicated by plus or plus-minus signs. This method has served adequately for comparison, is convenient, inexpensive and about as accurate as any of the other methods. For fine lung detail I send the patient out for a teleoroentgenogram.

DR. TARAN: How much reliance can be placed upon the angle of clearance as an aid in estimating the size of the left ventricle? If this angle of clearance over a period of time changed from 55 to 65 degrees would you consider this to be an indication of left ventricular enlargement?

DR. SCHWEDEL: I might consider the change to be due to an error in technic, and I believe errors are too frequent to make this method reliable as an index of left ventricular enlargement. Ten years ago, Dr. Harry Gross and I did a control series using this method, which included the use of a well constructed turntable, on about 160 school children. These were classified as to age, sex, weight and body build. The outlines were traced on cellophane and checked twice more. When the difference in all three checks was less than five degrees, the results were considered reliable and the figures averaged. We found no correlation between the angle of clearance and the size or shape of the heart. It seemed as if the varying factor was the distance between the posterior surface of the heart and the anterior contour of the spine.

Enlargement of the left ventricle results in increase in the length of its contour. Early such enlargement occurs downwards, or by increased rounding, termed a "fleshy" border by old-time roentgenologists. Later the enlargement involves the posterior portion, the inflow tract, which is the portion that is concerned in the angle of clearance. The only thing I will concede here is that a considerably enlarged left ventricle will usually fail to clear at an angle of 55 degrees, but by that time we do not need the angle of clearance to establish enlargement.

# Electrocardiographic Findings in Rheumatic Heart Disease*

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I DO not believe that the electrocardiogram shows features that are characteristic effects of rheumatic fever alone and therefore would not afford criteria for the diagnosis. On the other hand, it is certainly true that there are many instances in which the electrocardiogram may give the only sign of rheumatic activity. This is more apt to be true at the end than at the beginning of an acute attack. I have seen patients in whom there were no joint symptoms and who had only electrocardiographic changes. I remember one such patient, who came into the clinic ambulatory, with fever and with electrocardiographic changes, and we did not quite know why. She then developed a pericardial rub, and the reason for the electrocardiographic changes became evident. She later developed some joint symptoms which led to a diagnosis of rheumatic fever. But that case I think is exceptional. Usually the electrocardiogram is a manifestation of the disease which is diagnosed on the basis of other findings.

Rheumatic fever, of course, is much more extensive a disease than the rheumatic myocardial involvement which gives rise to the electrocardiographic changes. There are many other areas where rheumatic fever may attack besides the myocardium. The electrocardiogram should be considered as giving evidence of changes in myocardial function, and in rheumatic fever these functional changes are caused by certain types of pathological reaction to the rheumatic process.

There are in general three types of pathological changes: (1) There is a general inflammatory reaction with edema, interstitial swelling, leukocytosis and fibrinous degeneration. (2) There is the specific type of pathological change known as the Aschoff body, which is found in the interstitial tissue surrounding the small muscle bundles and particularly in the interstitial tissue surrounding the smaller arteries. (3) And then there is an arteritis which is also a definite rheumatic manifestation and which occurs in the coronary arteries as well as in other arteries of the body. We are particularly concerned with the coronary arteries where it causes an intimal thickening and eventually a fibrosis of the vessel wall.

Rheumatic endocarditis of itself probably does not affect the electrocardiogram, with the possible exception of that peculiar mural endocarditis occurring chiefly in the left auricle. This may give rise to auricular premature beats, auricular tachycardia and possibly, auricular fibrillation or flutter. Rheumatic valvulitis will not influence the electrocardiogram unless the valvular disease is severe enough to produce a mechanical change in the pressure in the ventricles, hypertrophy of one of the ventricles or auricles. The effects of myocardial disease upon the electrocardiogram, of course, depend upon the area of myocardium that

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is affected and on the character of the pathological change; that is, whether it results in irritation or a depression of the muscular tissue. The myocardial change is sometimes of a severe degenerative character though this is rare. The muscle fibers in such cases are degenerated and this produces a different type of electrocardiographic abnormality from that resulting from the usual inflammatory reaction with edema, infiltration and Aschoff bodies. Occasionally, the rheumatic arteritis may become so severe that it may occlude a coronary vessel and lead to thrombosis though this, too, is a rare occurrence.

Depending upon the effect on the muscle, we may find premature beats, paroxysmal tachycardia or other rhythm disturbances arising either in the auricles, the A-V node or in the ventricles. Actually, I am not aware that ventricular tachycardia has ever been observed in rheumatic fever though tachycardias with other foci have been repeatedly observed. Auricular fibrillation and flutter, and prolonged A-V conduction sometimes progressing to heart block with dropped beats or even to complete heart block may occur. Bundle branch block is a rare finding.

Certain changes in the QRS group and T wave may occur, such as low voltage of QRS, low voltage of T and changes in the electrical axis of QRS. There may be elevation of the S-T junction probably occurring as a result of acute degenerative changes and also diphasic or inverted T waves in leads I or II or both. These features usually are found during the active phase of the disease though they sometimes persist after other signs of activity have gone, even after the sedimentation rate has returned to normal.

Occasionally, changes in the T wave or in the P-R interval may persist after the disease has become inactive. It may be that in these cases there is fibrosis, which is

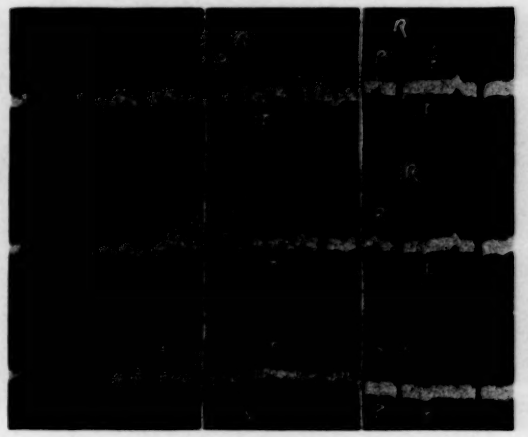


FIG. 1.

interfering with the function of the tissue. There is one interesting thing which has been observed about the A-V conduction time in rheumatic fever. Good-sized doses of atropin, such as might paralyze the vagus, will shorten the conduction time and this has been considered by some to indicate that a heightened vagus activity, an increased vagal tone, was responsible for the prolonged conduction time of rheumatic heart disease. This argument does not appeal to me because it is possible that the diseased tissue reacts abnormally to a normal vagal tone. The mere diminution of a vagal effect by atropin does not prove that the whole effect is due to the vagus.

Figure 1 shows records from three different patients. They all show a normal P-R interval, although in two of them it measures 0.20 second. There also is in the record on the left an elevation of the S-T junction. It is definitely elevated in leads I and II and very slightly in lead III. The patient had this electrocardiogram for a few days and then developed a pericardial rub, which did not surprise us because such S-T elevation is the recognized electrocardiographic sign of pericarditis. The central record shows nothing particularly significant in the QRS group except left axis deviation of slight degree, but the T wave is inverted in lead I,

FIG. 2.

inverted in lead II and upright in lead III. There is no S-T junction deviation. This curve appeared in the course of a rheumatic attack, and shows the character of the T wave changes which are sometimes found. The record on the right likewise shows only T wave changes. The QRS group is essentially normal. The T wave in lead I is iso-

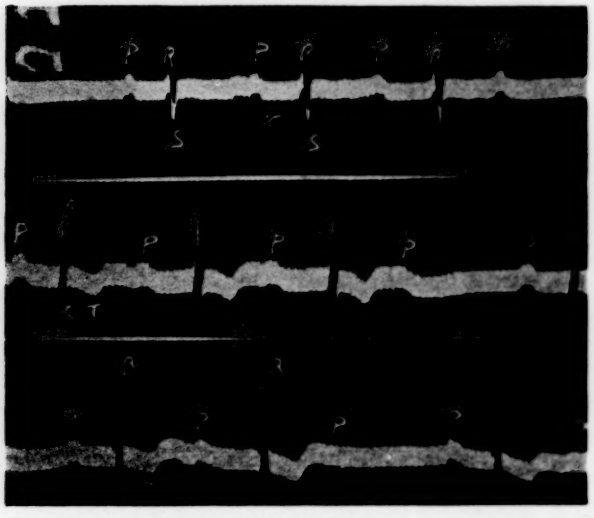


FIG. 3.

electric, or perhaps one might say, diphasic. In lead II, T is inverted and shows a slight upward convexity of the S-T segment which is like the upward convexity that we see in certain cases after coronary disease has caused degeneration. This type of curve often follows after the acute phase of pericarditis. In this case, it did not but arose spontaneously.

Figure 2 represents tracings of two patients with rheumatic pericarditis. The records were taken after the disease had been present for some time, and they both show T wave changes which look very much like the waves which you might see in association with the myodegeneration due to coronary disease. The record on the right has a very small downward T wave with upward convexity of the S-T segment. This patient also shows premature beats, which were probably of left ventricular origin. This one in lead II looks perhaps more like a nodal premature beat but I think they are both from below the branching of the bundle and on the left side.

Figure 3 shows a very common appearance in the course of rheumatic fever, i.e., heart block with dropped beats. It shows not a constantly prolonged P-R but one which is first 0.28 second, then becoming 0.32 second, then becoming 0.44 second, and then the P wave occurs without any ventricular complex indicating a blocked auricular impulse. This is the phenomenon which is found in a moderately high-grade disturbance of A-V conduction—the Wenckebach phenomenon. Here we see it again in lead II. Eventually, a P wave is blocked, and after the pause the A-V conduction resumes the shorter interval with which it started. This sort of thing often alternates with periods of occasional dropped

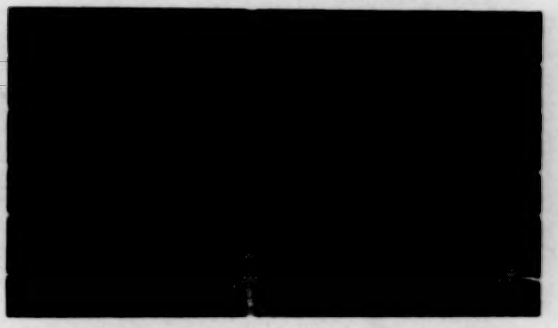


FIG. 4.

beats, or it may alternate with periods of regularly dropped beats. That is, there might be two auricular waves to one ventricular complex. It is not as high a grade of block as the two to one block and the characteristic thing is that it is transient. Clinically, it must be diagnosed from premature beats. This should be possible by noting the absence of any premature ventricular sound.

Figure 4 shows two records of a patient in the acute phase of rheumatic fever. The one on the left shows a prolonged P-R, which in lead I measures 0.24 second and in lead II 0.28 second, but in addition shows a low voltage of the QRS group, no wave being larger than R-2, which measures only 3.5 mm. In spite of this low voltage of QRS the T wave has a normal voltage, the largest amplitude being found in lead II where it reaches 3 mm. This same patient later developed a regular tachycardia with a rate of almost 100 per minute. No one suspected that there was anything but an ordinary sinus tachycardia, but the record seen on the right shows a nodal tachycardia to be present by the P wave which comes each time just after the QRS group. This is not an uncommon phenomenon in patients with rheumatic heart disease. I think it is more common than auricular tachycardia. You will notice that the T wave in these records is not abnormal in its form. There is one peculiar thing, however, seen in the second lead: the first, third and fifth T waves are larger than the second, fourth,

A B C

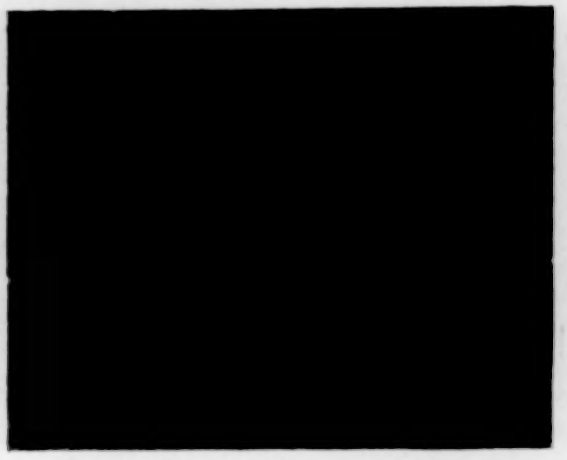
FIG. 5. A, record of May 20th; B, record of May 1st; C, record of April 22nd.

sixth, etc. In other words, there is an alternating variation in the height of the T wave which is considered to indicate a disturbance of myocardial function.

The next figures are serial records of New York Hospital patients with rheumatic fever. In Figure 5 the record on the right was obtained April 22nd from a patient at the beginning of an attack of acute rheumatic fever. The May record was obtained at a time when there was no fever but there was an increased sedimentation rate. It was a mild attack. This patient on April 22nd had a tachycardia with a rate of 100 and again it was a nodal tachycardia. The P wave shows as a notch just following QRS in two leads proving that this was a nodal tachycardia. The T wave was of average voltage. The bottom lead is the fourth lead, the precordial lead 4F. On May 1, there was a normal sinus rhythm. The rate was about 80 per minute and the T waves had a normal appearance in all four leads. However, the sedimentation rate was still increased at this time although fever was absent. You will notice the change in the appearance of the T wave. It has acquired more voltage. It is larger in amplitude than it was on April 22nd. Such changes are not infrequent and probably have some significance, in this case indicating a changed condition of the myocardium. A record was obtained on May 20th, a month after

A B

FIG. 6. A, record of June 4th; B, record of May 24th.



A B

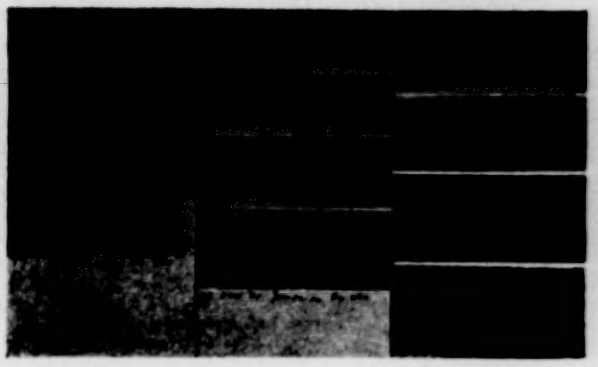
FIG. 7. The same case as Figure 6. A, record of July 23rd; B, record of June 25th.

the first one. At that time there was tachycardia, the rate being 100 per minute. The auricular-ventricular sequence was normal and the ventricular complex was normal. There was no fever; the joint symptoms had subsided, but the sedimentation rate was still increased.

Figure 6 was obtained from another patient. This patient on May 24th had an apical systolic murmur, fever and an increased sedimentation rate. At that time, as seen in the record on the right the A-V conduction time was prolonged, P-R measuring 0.24 second. The QRS group was not abnormal but the T wave in lead II had a peculiar notched appearance which is often the forerunner of an inversion of the T wave. In this case, however, the next record, obtained on June 4th, at which time the fever had subsided although the sedimentation rate was still increased, showed a normal A-V conduction time. There was a sinus arrhythmia. The T wave, however, had increased considerably in voltage and the peculiarity of $T_2$ was no longer present. $T_3$ had an unusual appearance in the slight elevation of the S-T junction and the downward peak at the end of T. The last beat in lead III was an auricular premature beat.

Figure 7 shows two more records of this same individual. The one on the right was obtained on June 25th. There were intermediate records which I left out because they did not show any significant changes. At that time the patient had a reappearance of arthritis and fever, very mild arthritis and not much fever. The sedimentation rate remained increased. The auricular-ventricular conduction time was again prolonged to 0.24 second; the QRS group was the same. The S-T junction in lead III was elevated a full millimeter, which was not so before. In lead II also there was an elevation of 1 mm. which was not previously present. Besides the change in the S-T junction, the voltage of T in Figure 6 was much larger than in Figure 7. The change in voltage of T and in the elevation of the S-T junction indicated a change in the state of the myocardium. A record was obtained July 23rd at which time the patient was about ready to be sent home. Though he had no fever, the sedimentation rate was still increased. The S-T elevation, which was present in lead II had been considerably reduced and in lead III the S-T elevation had disappeared; the voltage of T had slightly increased. The fourth lead contributed nothing in this case.

Figure 8 is a third case. The first record at the right was made when the patient was ambulatory and did not demonstrate any acute rheumatic manifestations. It may



A B C

FIG. 8. A, record before acute attack; B, record of January 14th; C, record of January 25th.

A B C

FIG. 9. The same case as Figure 8. A, record of February 23rd; B, record of February 11th; C, record of February 4th.

serve as a control. Four leads are shown and there is nothing unusual about it except the left axis deviation. The patient had murmurs which led to a diagnosis of aortic stenosis and insufficiency with mitral insufficiency. He had a very large heart and was a man of about forty-five years of age. January 14th was a couple of days after the beginning of an acute rheumatic attack which did not make itself very evident in the joints but which was associated with definite fever and increased sedimentation rate. If we had only seen this record without having seen the previous one we might hesitate to say that that T wave was abnormal, but having seen the earlier record, I think it is proper to say that this is abnormal. The S-T segment in lead II is somewhat elevated, and the T wave does not have the normal type of curve concave upward toward an apex, which we see in lead I of this record and in lead II of the previous one. The large upward T wave in lead IV is also unusual. There is no change in the P-R conduction time. The tracing taken on January 25th, seen on the left while fever was still present and the sedimentation rate increased, showed abnormal T waves in lead II with inversion and perhaps a little coving of the S-T segment, an upward convexity. There was no change during this time in the murmurs that were found over the precordium. They remained the same.

In Figure 9 the record on the right was obtained on February 4th, nine days later. The T wave in lead I is upward; the T wave in lead II has assumed a form which you might consider normal if you had not seen the earliest record. I think, however, it might be called normal. There is no significant abnormality in this record and the P-R interval is normal. There was no fever at this time and the sedimentation rate was increased. On February 11th, seven days later, fever had reappeared. The record shows a change in $T_2$. It becomes diphasic. In lead III a ventricular premature beat makes its appearance. Twelve days later, on February 23rd, there is no fever. The sedimentation rate is still increased. The T wave of this record in lead II appears about as on February 11th.

In Figure 10 we see on the right the record of March 8th, two weeks later. During this time there had been no more fever and no more joint manifestations. The process was apparently subsiding but the sedimentation rate was still increased. The T wave in leads II and IV is returning somewhat more towards normal. Here is an example of how the diagnosis of activity of rheumatic fever may be aided by the electrocardiogram. There was nothing in this patient's clinical

A B C

FIG. 10. The same case as Figures 8 and 9. A, record of April 3rd; B, record of March 27th; C, record of March 8th.

appearance between March 8th and April 3rd to indicate that his condition was not progressively improving. Yet this T wave, which was essentially normal on March 8th, has become definitely abnormal on March 27th and on April 3rd is still definitely abnormal. At this time the physicians were so impressed with the fact that the man had clinically recovered from his rheumatic fever that they sent him home with this progressing abnormality in the T wave. It seems to me that this was an indication of activity of the rheumatic process and that he should have been kept in the hospital until the T wave returned to normal or stopped showing progressive changes. These electrocardiographic changes are found with a frequency which has never been accurately determined because the frequency with which you find these things is going to depend upon how often you look for them.

There are only two series of cases in which daily records have been taken. Dr. Cohn took daily records of thirty-seven cases. Dr. Master and Dr. Jaffe took daily records of sixty-three cases. Dr. Cohn found 93 per cent, which is all but two of his cases, to have some form of abnormality of the electrocardiogram during the course of their illness. Master and Jaffe found 100 per cent of their cases to have some significant change in the electrocardiogram. This includes arrhythmia, form changes and P-R changes. If you look for it daily, you will find electrocardiographic changes in practically 100 per cent of rheumatic patients. The percentage of findings are interesting in different series. They read as follows: 100, 100, 95, 94, 93, 92, 90, 94, 70, 67, 40, 22. In the last group, electrocardiographic changes were found in only 22 per cent of patients who had chorea, and they had only about three records from each patient in the course of a number of months. That is why they found only 22 per cent to show any abnormality. If they had taken more frequent records, I am sure that they would have found more frequent changes.

The relative frequency of P-R changes and T wave changes is of interest, but is found nowhere in the literature. The authors have not attempted to distinguish statistically between changes in P-R and changes in T waves. True, it is not very important, for the findings indicate activity of the disease in either case. But it may be a matter of more than academic interest whether the activity lies in the A-V conducting tissue or in the ventricular myocardium which produces the T wave. Master and Jaffe, who have the largest number of daily records of patients, found increased P-R time in 65 per cent, and in one-third of these the conduction disturbance went to the degree of dropped beats. They did not report any cases of complete heart block. Dr. Cohn in his thirty-seven cases found complete heart block in one case. He found bundle branch block in three cases. Master and Jaffe did not find it at all in their larger series. Therefore, it must be an infrequent happening. Master and Jaffe found abnormal S-T and T wave changes in 85 per cent of their cases. Cohn does not distinguish statistically between the two types of change. The

arrhythmias occur with a variable frequency in the different series, but I think that Cohn's findings on the arrhythmias are the best reported. In thirty-seven cases he found auricular premature beats ten times, not in ten cases but ten times; auricular fibrillation five times; auricular flutter once; auricular tachycardia five times. He found sino-auricular block once. He found A-V nodal premature contractions three times. He noticed A-V nodal rhythm five times. This does not give you the idea of the number of cases that developed these things but only the frequency of occurrence in the series of cases. He found prolonged P-R and heart block combined ten times. A-V rhythm is perhaps one of the most common types of arrhythmia that we encounter, if you exclude the dropped beats which are associated with the higher grades of heart block.

With less frequent records, a different picture is presented. Dr. May G. Wilson reports on fifty-four hospital cases with acute rheumatic fever. She found prolonged P-R or abnormal T wave or elevation of S-T or some other arrhythmia in 33 per cent. In these cases, records were taken about once a week. In 860 ambulatory patients whose records were taken occasionally, 22 per cent showed some sort of electrocardiographic abnormality. It is important to bear in mind that these electrocardiographic abnormalities occasionally may be found when the patient does not show any other evidence of rheumatic activity though, as I said before, the sedimentation rate is usually coincidentally affected. When electrocardiographic abnormality occurs without the sedimentation rate being affected, I would be inclined to attribute it to a fibrotic myocardial change rather than to an acute inflammatory reaction. In most patients, the disturbance of the record entirely disappears when the disease disappears and only a small percentage is found to have any abnormality in the electrocardiogram after the acute phase of the disease. Right or left axis deviation of QRS affords an exception here which might be due to hypertrophy of one or the other ventricle of the heart.

### DISCUSSION

DR. TARAN: It is commonly taught that there are three distinct types of disturbances in the electrocardiogram in acute heart disease; one refers to rhythm, one refers to muscle change, and the last refers to possible changes in the size of the heart, as ventricular strain. Are there any changes in the electrocardiogram that might be significant of disturbances in the functional integrity of the heart? For instance, in acute infarction one may find that the systolic period of the heart is increased. In hypocalcemia, in hypopotassium states, when there is a disturbance in the functional dynamics of the heart, there is also a disturbance in the sequence of events in the cardiac cycle. Can this disturbance of sequence of events be considered a criterion of an acute inflammatory process of the heart muscle itself?

DR. PARDEE: Yes, I think so, definitely. I always look upon the electrocardiogram as a record of a physiological function of the heart, one which is unrelated to all other functions except perhaps the chemistry of the heart muscle. That, after all, is the basic function which produces the electrical potential. In the course of disease there are physiological changes in the muscle, changes due to the inflammatory reaction which is present, to the edema, to the encroachment upon the muscle bundles by pressure, and I do not know what the Aschoff bodies do, but they probably represent chemical irritation of some sort. I think that all those things, any one of them, may change the electrocardiogram. It may change the S-T junction or the T wave, or

it may cause an arrhythmia of what I call the irritative type, the premature beat or a tachycardia, no matter where it occurs in the heart. Only when we have permanent structural changes do we get permanent electrocardiographic changes. That is why I think that all of these things should be looked at as being on the physiological level. They are due to changes which we can see only occasionally with a microscope.

Edema is the main change which we can see. Fever itself does not seem to cause this type of electrocardiographic change. I do not think that these patients with acute rheumatic fever are usually subject to disturbances in their calcium metabolism, so I question if that could be used as anything but an illustration of a type of abnormality that can change the electrocardiogram. I think the lesson from all this is that in following a patient with acute rheumatic fever it is advisable to take electrocardiographic records from time to time, especially approaching the time when you think it is all over and the patient is getting better. If you then find abnormalities in the T wave or in the conduction time, I think this is an indication that it is not over; I think that the percentage of cases that come through rheumatic fever with permanent electrocardiographic changes is very small, perhaps 1 or 2 per cent and that they have this because of fibrosis.

DR. GELLER: It was my impression as I saw those slides that some of those T waves showing changes in voltage also appeared peaked and symmetrical. The T's were definitely abnormal in that they were peaked and symmetrical rather than normal and asymmetrical.

DR. PARDEE: I think that that is a very interesting observation and perhaps one that I have not appreciated. I think that this may be a new feature of the abnormal T wave that we may recognize as being due to myocardial abnormality.

DR. GOERNER: In rheumatic fever do you ever see changes in the S-T and T waves in the precordial leads that are not evident in the other leads?

DR. PARDEE: Yes, I think you do. These records that are shown here happen to have normal precordial leads in each case, even when the limb leads are abnormal, but there are other cases in which the precordial leads are abnormal and the limb leads are normal. The frequency of that I could not tell you. It has never been studied to my knowledge. Although I know of one series of cases reported by Levy and Turner in which they studied precordial leads, yet they were concerned more with serial changes in the same patient. I do not think they reported on the number of precordial leads that were abnormal when the limb leads were normal. They were concerned with changes in precordial leads from one time to another. However, I am sure from what I know of the electrocardiogram that there must be many cases that will show an abnormality in the precordial lead and yet have normal limb leads.

DR. GOERNER: Would you consider a sharp inversion of the T wave in precordial leads in a thirteen-year old child significant?

DR. PARDEE: I would want to be sure that it was obtained at position four because the placement of the precordial electrode is one of the biggest stumbling blocks in electrocardiographic technic. If it was not placed near the sternum, if it was at the apex, the child being thirteen years old, I would think that an inverted T wave in such a patient would certainly mean an abnormality of the myocardium of some sort.

DR. GOERNER: Even as an isolated finding?

DR. PARDEE: Yes.

DR. WATTS: Then we are to infer from your answer to the last question that there are precordial leads with the T wave inversion that can be considered normal? In

other words, T wave inversion, possibly more to the right than to the left of the apex, can be considered within the limits of normal?

DR. PARDEE: Absolutely so in children. In adults, particularly in women of the hyposthenic type, leads from near the sternum, position II or even position III in children, may show an inverted T wave in individuals that are, I believe, normal. And in adults, in women of the hyposthenic type, a $T_3$ may be inverted.

DR. WATTS: And five and six?

DR. PARDEE: But not in four or five.

DR. WATTS: When you see a bundle branch block on the electrocardiogram of a patient whose past history is unfamiliar to you or when the patient denies all previous illness, do you interpret such a finding as myocardial injury and damage or can that be within the limits of normal?

DR. PARDEE: I would feel, if I saw a record with bundle branch block, that the patient's heart was abnormal, that is, it had some pathological change. I understand that Willius has advanced the idea that it may be a normal phenomenon. I cannot understand it as such.

DR. WATTS: In the army we often observed bundle branch block in apparently normal individuals, often times men who had previously been athletes and had had no sign of heart disease. It would always become a great problem as to whether that patient should be discharged from the army on that simple finding. As a matter of fact, the principle was followed that they were discharged, but it always used to bother me.

DR. TARAN: Is it not conceivable that those were congenital findings and did not interfere with the function of the heart, permitting these individuals to become athletes. From the functional standpoint, therefore, they may be considered as normal.

DR. PARDEE: That bundle branch block may be a congenital anomaly in association with other congenital disease is well known, but the type of case referred to, I understood, had no other evidence of heart disease. As an isolated congenital anomaly, I am not acquainted with it. That may be Willius' contention. It is certainly obvious that people can have bundle branch block and have no apparent impairment of their cardiac reserve. Why should they? It makes very little difference to the heart function whether one ventricle goes off two or three-hundredths of a second after its normal time. So I can understand a very sharply localized disease affecting a bundle branch and not affecting much else of the myocardium, which might not cause the heart to be below normal in its functional capacity

There are many such patients. The first time I heard of this was many years ago. I received an electrocardiogram from the West. A doctor had bought an electrocardiographic machine and had taken a trial record of his brother who was thirty-five years of age. It showed right bundle branch block. He sent it to me in consternation. What could he do about it? That has been cropping up ever since; a great deal of it was found in army work. All we know about it would lead us to believe that it is due to a small focus of disease.

DR. BATTRO: I have just published a paper on the precordial leads of children. We found that the inverted T wave in the precordial leads in normal children are different in form from the inverted T wave in abnormal cases. The ascending limb of the T wave in normal children is long and reaches or, in fact, rises above the iso-electric line, whereas in the abnormal heart it does not reach this point.

DR. PARDEE: Very interesting. I did not know that.

DR. BATTRO: And after ten years of age we never found a T wave inversion in the precordial leads IV, V or VI.

# Case Reports

## Histoplasmosis

### *Report of Diagnosis from Biopsy of Cutaneous Nodules**

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CHICAGO, ILLINOIS

WORKING independently, Major Leishman in May, 1903, and Captain Donovan in July, 1903, identified and described the organism responsible for kala azar. Armed with this knowledge, Darling[1] of the U. S. Public Health Service in Panama, reasoned that there should exist in that region of the New World a disease which has such widespread distribution in the tropics of the Near and Far East. In 1905, while examining the lungs, liver, spleen and bone marrow of a Martinique negro, he encountered numerous tubercles, presumably miliary tuberculosis, in which no acid fast organisms could be demonstrated. By the use of other stains, he observed intense invasion of endothelial cells by small, round or ovoid bodies, about three microns in diameter, with refractile peripheries and non-homogeneous internal structures. It is to the credit of Darling that he did not accept these organisms as Leishman-Donovan bodies and that, failing to find with polychrome methylene blue-eosin stains the chromatin rods characterizing the latter, he concluded that he had discovered an hitherto unknown organism responsible for a fatal infection in a native of this hemisphere. He regarded the organism as protozoon in character, an opinion concurred in by Major Ronald Ross, and named it Histoplasma capsulatum and the disease histoplasmosis. In 1906, two additional cases reported in detail in 1908[2] were found. During a period of three years, among 33,000 admissions to Ancon Hospital, no additional cases were encountered.

It was not until 1925 that a fourth case was observed when Riley and Watson[3] found the disease in a fifty-two-year old German-born female patient, who had not been outside of Minnesota for the last forty-four years. Generalized lymphadenopathy, splenomegaly and cirrhosis of the liver were present. With routine hematoxylin and eosin stains, the invading organisms were at first entirely overlooked. They were clearly revealed later with Weigert-Gram, Giemsa, Bensley's aniline, acid fuchsin and methyl green, and phosphotungstic acid—hematoxylin stains. Initially they were considered to be Leishman-Donovan bodies, but were later shown to be identical with Darling's Histoplasma capsulatum. Watson[4] published a detailed account of the histologic findings with special discussion of the origin of the phagocytic cells.

Because of its close resemblance to the Leishman-Donovan body, Darling, Ross and others considered Histoplasma capsulatum to be a protozoon. However, Rocha-Lima[5] as early as 1912, after studying Darling's material, believed that it was a yeast-like fungus, an opinion confirmed when De Monbreun[6] succeeded in growing the organism *in vitro* in a yeast-like form typical of fungus, with production of

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A B

FIG. 1. X-ray of lungs. A, April, 1943, slight increase of density at right base; B, four weeks later, generalized increase in lung markings. Diagnosis: x-ray, low grade inflammatory infection, possibly blastomycosis.

mycelia and spores. Conant,[7] in his comprehensive study of its growth characteristics, classified it in the Moniliaceae group of Fungi imperfecti. The yeast-like form alone is pathogenic to humans, has never been recovered outside of the human body, and on artificial media exhibits typical spinate or barbed forms (Fig. 3A.) as contrasted with the mycelial type which has been recovered from dogs, possibly rats and other rodents. Neither form has been recovered outside of mammalian bodies. By appropriate cultural methods, either form can be converted to the other.

Since the fungus does not appear to exist freely in nature, nothing is known of the portal of entry or method of infection, but as the entire gastrointestinal tract, respiratory system and skin are commonly involved, they presumably constitute the most frequent sites of infection. The disease is apparently not very contagious as there are no published reports on consanguinity, contact, or exposure resulting in infection. Demonstration of the fungous character of the organism, as contrasted with the protozoon nature of the Leishman-Donovan body, detracts from the value of Patton's[8] important observation that the latter, in all stages of development, may be found in infected bed-bugs. Furthermore, in contrast to histoplasmosis, it is reported that in kala-azar the cutaneous and systemic forms of the disease do not manifest themselves in the same individual, at any rate not at the same time.

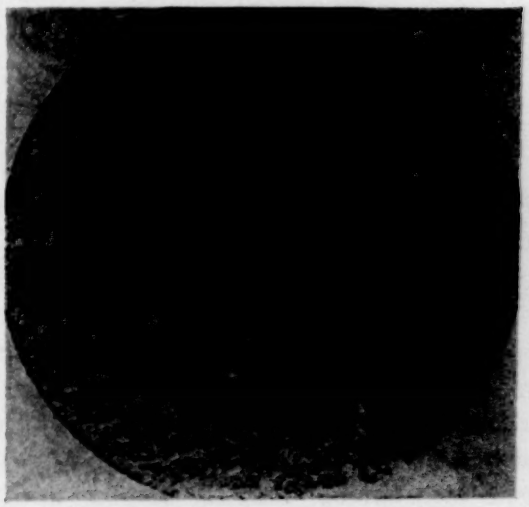


FIG. 2. Low power section of cutaneous nodule obtained by biopsy.

Since there have recently been numerous excellent and detailed accounts of the manifestations of histoplasmosis, reviewing

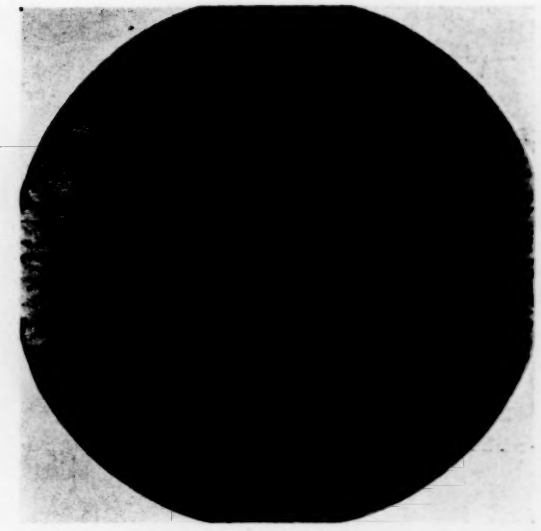


FIG. 3. A, growth of Histoplasma capsulatum from blood culture on blood agar plate at room temperature, showing characteristic spinate form of yeast form pathogenic to man.

present knowledge of sex incidence, age, occupation, methods of diagnosis, incidence and distribution, as well as full descriptions of the disease in the human body, no attempt will be made to recapitulate these facts. Broders et al.[9] published a review of the literature with a case report of vegetative endocarditis of this origin. Parsons and Zarafonetis[10] have more recently presented a complete bibliography and extensive discussion, including summaries of seventy-one published cases with a detailed description of ten of these.

The increased number of cases reported, especially since 1936, is due in all probability to more general recognition of the disease. Clinically this has been accomplished by more frequent sternal or tibial punctures, blood smears, biopsy, and in particular by realization of the slow growth of the organism both at incubator and room temperatures (thus avoiding the practice of too rapid discarding of cultures, since growth may appear as late as twelve or even eighteen days). Pathologists, bacteriologists and parasitologists have also become more familiar with the material obtained by culture or at postmortem and consequently

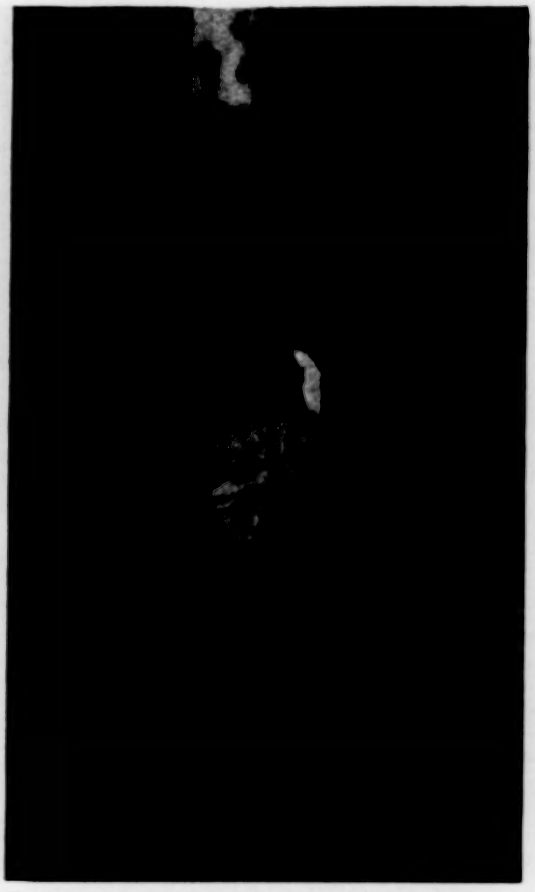


FIG. 3. B, growth on Sabouraud's medium at room temperature.

have recognized the organism more frequently. A diagnostic cutaneous test by intradermal injection of the filtrate of a broth culture of the organism has also been reported.[11]

Histoplasmosis until recently has been considered an invariably fatal disease. However, there have been recent reports of healed, calcified lesions, ostensibly tuberculosis, which after careful examination were considered to be healed histoplasmosis. Parsons and Zarafanetis[10] described apparent recovery from local, ulcerated lesions following x-ray therapy, and in cases in which the infection was limited to lymph nodes, cure by the use of antimony preparations and by diamidine.

## CASE REPORT

A seventy-two year old woman, who had been under our medical care for many years,

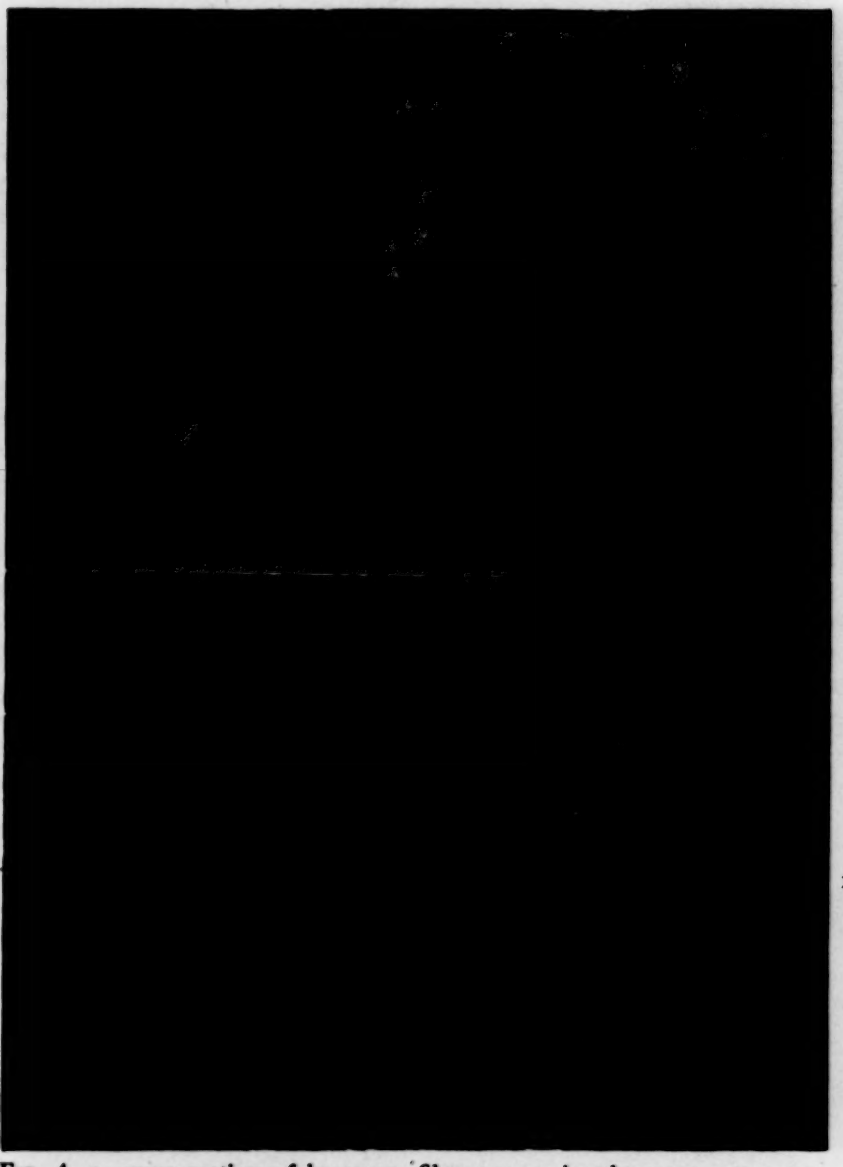



FIG. 4. A, gross section of lungs; B, fibrocaseous involvement more generalized and uniform than in pulmonary or miliary tuberculosis. × 73.

came to the office January 4, 1943, for a routine, semi-annual examination before going to Florida. She had always been in excellent health, was an alert, active person taking part in many civic and community affairs, and except for a known diverticulum of the esophagus, had had no illness or abnormality. Thorough questioning and examination at that time revealed no indication of disease.

On her return in April, 1943, she presented a striking picture of advanced Addison's disease; appearing thin, with marked pigmentation of the entire body, especially noticeable on the exposed portions, and was obviously weak and desperately ill. Her symptoms were anorexia, nausea and vomiting, diarrhea, weakness and loss of ten pounds in weight. History revealed that she and her husband had what was presumed to be the then prevalent virus enterocolitis (intestinal influenza) from which he had promptly recovered. She, however, had a chill at the onset, with fever lasting for five days, after which a persistent, non-productive cough developed. In spite of medication and a carefully maintained colitis-type diet, all symptoms persisted and she was sent immediately to the Presbyterian Hospital. Remembering that her sister had died two years previously of peri-

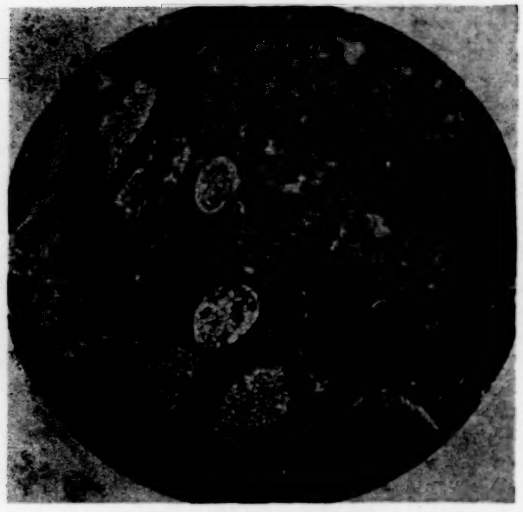
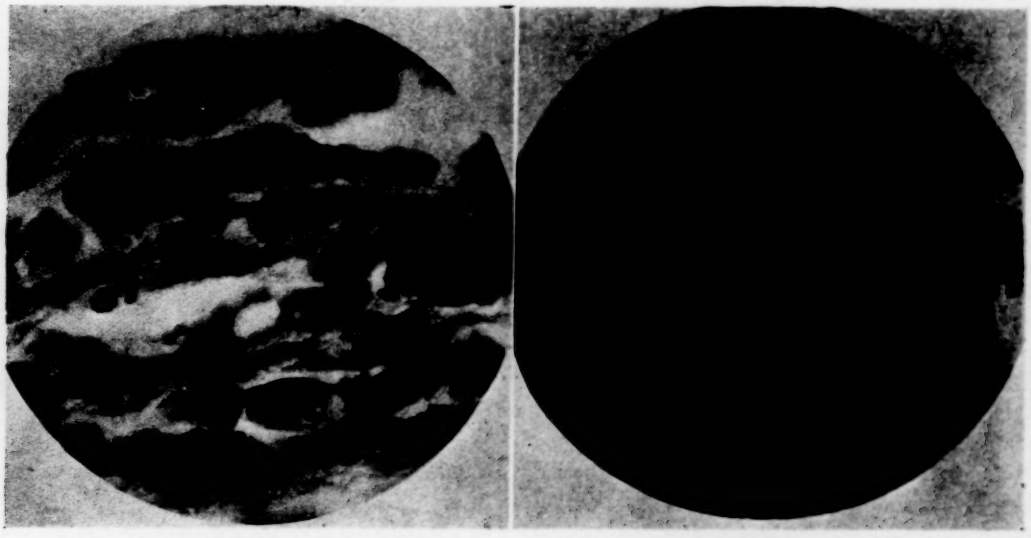


FIG. 5. Liver, round and ovoid bodies both intracellular and extracellular.

arteritis nodosa, after a prolonged illness with fever of obscure origin and symptoms in many respects similar to those of the patient, this diagnosis was primarily considered. On admission she had fever ranging from 100°F. to 103°F., which persisted until death. Examination revealed a tender mass in the right upper quadrant, a gallbladder filled with stones and failing to concentrate dye, normal gastric acidity, blood pressure 150/80, confirmation of esophageal diverticulum, white blood cell count 4,500 with normal differential, and normal chest x-ray. (Fig. 1A.) No amebae were found in examination of numerous stools and serological tests for undulant fever and typhoid, as well as the Kahn test, were normal. In spite of her cough, no sputum was ever obtained.

She was allowed to go home, where she was seen frequently. But as her condition became progressively unfavorable, she returned to the Presbyterian Hospital one month later, May 18th, having lost an additional twelve pounds, with persistence of cough, anorexia and nausea. Diarrhea had ceased. There were râles at the base of each lung posteriorly. *X*-ray (Fig. 1B) of her chest showed marked increase in density in both lungs as compared with the film taken one month previously, the markings being suggestive of a low-grade infection, possibly blastomycosis. Blood pressure was approximately as before, 158/86. At this time she had in the web of the right hand between the thumb and first finger, a hard, umbilicated nodule or papule which was very tender and painful and in spite of her other discomforts, she complained bitterly about it and maintained that it was very important. Four days after admission, her nurse reported a crop of similar lesions about her neck and shoulders posteriorly and on the following day a large number, perhaps fifty, appeared rather generally distributed over the body. They were very painful, especially with pressure, so that she could not be comfortable in any position. Sections were obtained by biopsy (Fig. 2)



A B

FIG. 6. Adrenal cortex; A, high power; B, oil immersion, invasion of cells and extensive caseation necrosis of tissue.

(J. H. M.). The pathological report showed numerous fungus-like organisms were present, diagnosis blastomycosis. Not satisfied with this, a second biopsy was performed and the material obtained was studied by examination of stained, macerated tissue on slides, and by sections, each method revealing an organism identified as Histoplasma capsulatum. Culture of the fresh material later grew an identical body. The day on which the second biopsy was performed, positive blood cultures appeared on Sabouraud's medium after nine days' growth at room temperature and the characteristic yeastlike form with spinate configuration (Fig. 3) confirmed the tissue biopsy findings, as did subsequent growth from this latter source. No specific (antimony) therapy was instituted and death occurred June 20th.

Complete autopsy confirmed the antemortem diagnosis of histoplasmosis. The entire reticuloendothelial system was involved. The anatomic diagnosis follows: Histoplasmosis of lungs, liver, spleen, kidneys, adrenal glands, trachea, thymic fat, skin; also tracheobronchial, parapancreatic and mesenteric lymph nodes; extensive fibroid mycosis of the lungs; generalized embolic papular and ulceropapular mycosis of the skin; extensive coagulation necrosis of the adrenal glands; moderate brown pigmentation of the body, especially the exposed portions of the upper extremities; mycotic focal glomerulonephritis was evident with minute focal mycotic granulomas of the liver and spleen and focal necrosis of the liver, as well as subacute hyperplasia of the spleen. The other findings were not relevant.

## COMMENT

Of particular interest, considering the striking resemblance to Addison's disease, is the extensive involvement of the adrenal glands and the presence of extensive coagulation necrosis. No normal adrenal cortical tissue remained and where isolated groups of cortical cells could be identified, they appeared to be undergoing coagulation or hyalin necrosis. (Fig. VI A and B.) Furthermore, despite the clinical picture, as well as the gross and microscopic evidence of almost total adrenal cortical destruction, the blood pressure remained elevated throughout (148/74) to within thirty-six hours of death.

In view of the extensive and generalized embolic cutaneous papular lesions in this patient, it is of interest to record that Darling, in Case 3, notes "the presence of cutaneous papules."

## SUMMARY

A case on first impression presenting a syndrome resembling acute adrenal cortical insufficiency, and later that of a generalized fungous infection presumably blastomycosis, was demonstrated antemortem by material obtained from biopsy to be one of histoplasmosis.

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# Congestive Heart Failure Arising from Uncontrolled Auricular Fibrillation in the Otherwise Normal Heart

## Follow-up Notes on a Previously Reported Case*

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THAT auricular fibrillation may develop in an otherwise normal heart and without any discoverable cause is now a generally accepted fact. However, that prolonged overwork resulting from uncontrolled auricular fibrillation may of itself cause congestive failure in a heart free of organic disease is less generally recognized. The following case, which has been the subject of a previous report,[1] is now presented with additional notes extending over a period of eleven years.

### CASE REPORTS

CASE 1. A woman aged forty-three years, from whose history there was excluded rheumatic, hypertensive, thyrotoxic or any other heart disease, suddenly developed auricular fibrillation followed three months later by severe congestive failure. The extent of the cardiac enlargement and pulmonary congestion is shown in Fig. 1.

After one week of bed rest and digitalization, normal rhythm was restored on June 18, 1935, by means of quinidine sulphate. Small maintenance doses of quinidine were continued for two days. All medication was then stopped and from July 20, 1935, to the day of the last examination, July 17, 1946, no treatment was administered.

During this period of more than eleven years the patient has remained in perfect health and has carried on an exceptionally active social and economic life. Frequent physical, radiological and electrocardiographic examinations have failed to disclose any significant deviations from the normal. Figures 2, 3, 4, and 5 show the chest films and electrocardiograms recorded respectively in 1941 and at the last observation in 1946.

This case clearly demonstrates that severe congestive failure of a normal heart may be brought about by overwork resulting from uncontrolled auricular fibrillation. It also shows that in this type of case a complete and apparently permanent cure may be effected through the restoration of normal rhythm.

At the time of the first communication in 1937, the only similar case found in the literature was that of Parkinson and Campbell.[2] Since then two others have been reported, one by Levine and Beeson[3] and one by Trotter and Eden.[4] In the latter instance the arrhythmia was abolished by total thyroidectomy. The patient had been under observation over a period of eight years, and although the rate was controlled with digitalis therapy, the heart continued to enlarge and several episodes of congestive failure occurred. Following total thyroidectomy, regular sinus rhythm returned and the heart became normal in size. At no time before or after the operation were signs of thyrotoxicosis demonstrated and the thyroid gland was entirely normal macroscopically

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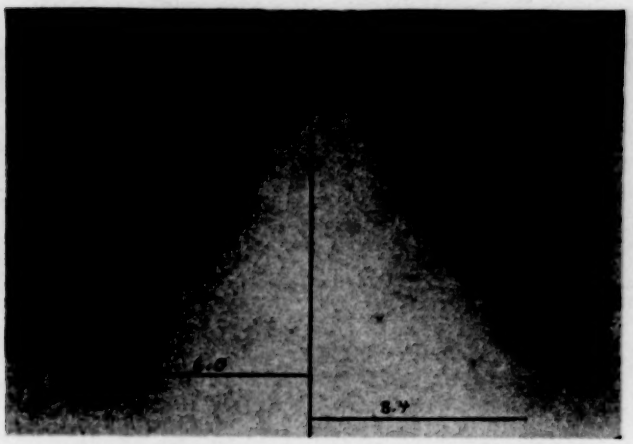


FIG. 1. Film taken June 8, 1935, showing passive congestion and fluid in pleural cavities. The transverse diameter of the cardiac shadow measures 14.4 cm.

FIG. 2. Film taken September 2, 1941, showing no passive congestion and heart normal in size, shape and position. The transverse diameter of the cardiac shadow now measures 11.6 cm.

and microscopically. Presumably total thyroidectomy rather than quinidine therapy was elected in this case because of the prolonged history of auricular fibrillation and repeated attacks of congestive failure. However, Parkinson and Campbell's case which was analogous in duration and repeated episodes of failure responded equally well to quinidine therapy.

In the cases cited above the pathological processes induced by auricular fibrillation appear to have been completely reversed by measures which controlled the cardiac rate and permanently abolished the arrhythmia. However, in similar instances if digitalis alone is used and no effort is made to restore normal rhythm, the continued heart strain and consequent cardiac enlargement may result in chronic and eventually fatal myocardial insufficiency.

Such a case has been reported by Gossage and Hicks.[5] A man aged twenty-three years

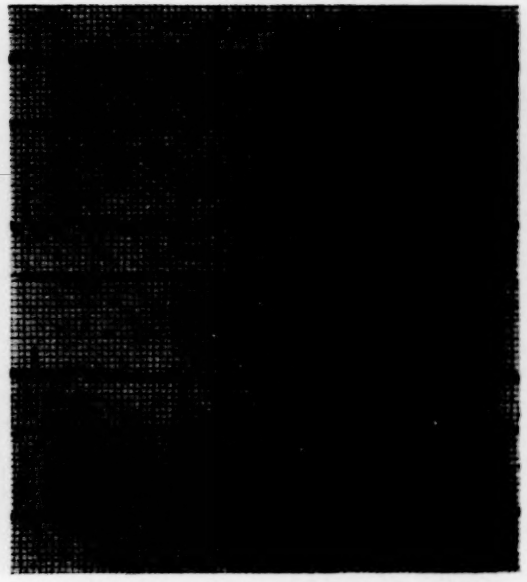


FIG. 3. Electrocardiogram taken September 2, 1941, showing normal tracing. Ventricular rate, 65.

during a coughing spell developed auricular fibrillation. A few hours after onset examination revealed the heart not enlarged and otherwise normal except for the arrhythmia. Although the rate was controlled by digitalis therapy, frequent examinations indicated gradual cardiac enlargement and one year after the onset of auricular fibrillation the apex beat was found to be in the sixth interspace, two inches external to the nipple line. Gross peripheral edema never developed but at varied intervals there were spells of precordial pain, palpitation and dyspnea. One and one-half years after the onset, while running across the road after a friend, the patient fell dead.

Autopsy revealed a large heart (600 Gm.) with completely normal arteries and valves. Numerous sections taken from various parts of cardiac tissues failed to reveal any abnormalities. The muscle fibers looked healthy, there were no collections of leukocytes and no increase of fibrous tissue.

It is possible that many similar cases remain unrecognized even at autopsy, due to complications which develop after a prolonged period of fibrillation and failure. The following case is an illustration.

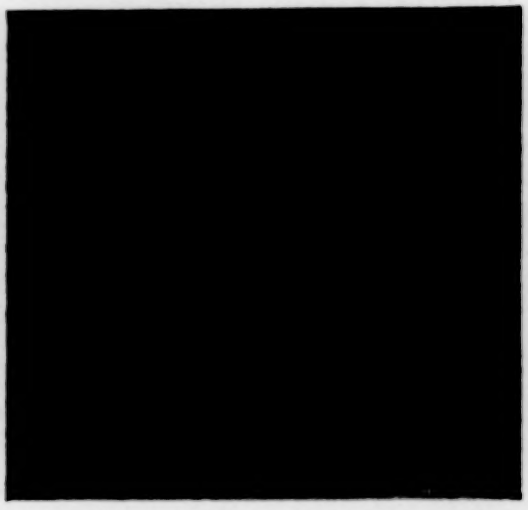
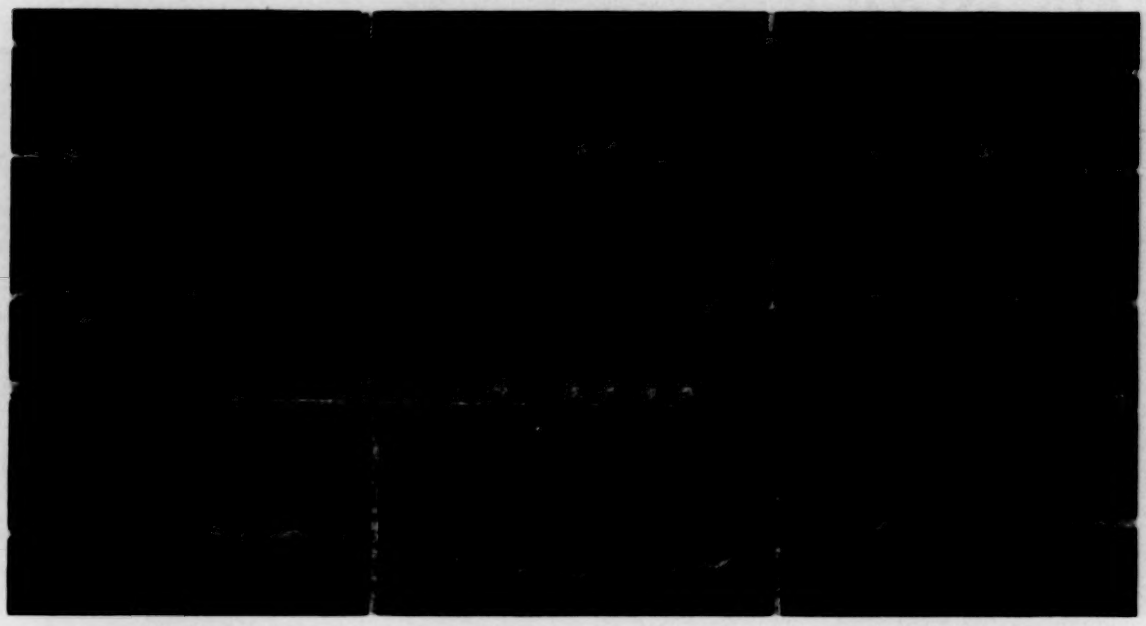


FIG. 4. Film taken July 17, 1946, showing no passive congestion and heart normal in size, shape and position.

CASE II. A man, aged forty-seven years, was first seen in April, 1936. His complaints were palpitation of some four years' duration, numbness of the extremities and dizzy spells. Examination disclosed a heart of normal size, a totally irregular rhythm and electrocardiographic evidence of auricular fibrillation. The blood pressure readings, the basal metabolic rate, and the blood and urine were essentially normal. During the ensuing years the heart remained in persistent auricular fibrillation and the rate was only poorly controlled by digitalization. After several episodes of congestive failure the patient died January 1, 1940 from pulmonary embolism.

During the final months of life he had suffered numerous embolic accidents involving the lungs, the brain, the extremities, and perhaps also a small branch of the left coronary artery. At autopsy the heart was found greatly enlarged (760 Gm.) The valves were normal. The coronary ostia were freely patent and serial sections of the coronary arteries showed only a slight degree of arteriosclerotic thickening. No areas of significant narrowing or complete occlusion were found. The myocardium was normal macroscopically and microscopically with the exception of a small area of thinning near the apex. This may have been the result of an occlusion (embolic?) of a small branch of the left coronary artery although no direct evidence of such an occlusion was found in any of the numerous sections studied. Other embolic lesions were



Standard Leads I, II, III | Unipolar Precordial Leads $V_2$, $V_4$, $V_6$ | Unipolar Limb Leads AVL, AVR, AVF

FIG. 5.

found in the left kidney, both posterior tibial arteries (canalized thrombotic emboli), the brain (in the region of the right internal capsule), and the lungs (bilateral pulmonary embolism). The multiple emboli undoubtedly originated from mural thrombi which were present in the left atrium and both ventricles. With the exception of an infarct in the left kidney no renal lesions were found. No arteriolar thickening was present to justify the assumption of hypertensive disease as an explanation for the extreme cardiac enlargement or for the onset of auricular fibrillation. The thyroid showed slight interstitial fibrosis, but no hyperplasia or lymphocytic collections were present.

This case illustrates the difficulties attending the attempt to determine the underlying etiological factors in a cardiopathy of this nature. Certainly at the time when auricular fibrillation was first noted none of the known causes usually responsible for such an arrhythmia could be demonstrated, and none could be definitely established at autopsy. It is not improbable that the arrhythmia was of itself the prime factor.

## SUMMARY AND CONCLUSION

Follow-up notes extending over a period of eleven years are presented on a previously reported case. These observations together with others cited from the literature offer convincing evidence that overwork from uncontrolled auricular fibrillation may of itself produce cardiac enlargement and congestive failure in a heart otherwise free of organic disease. The importance of recognizing the functional nature of the arrhythmia in such cases and of establishing normal rhythm is pointed out.

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# Book Review

**Biochemistry of Cancer.** By Jesse P. Greenstein, Head Biochemist, National Cancer Institute, National Institute of Health, United States Public Health Service. Pp. VIII + 389, with 39 figures and 104 tables. New York, 1947. Academic Press, Inc. *Price* $7.80.

The author has in this volume made available a comprehensive and authoritative summary and analysis of the contributions of the biochemical approach to the cancer problem. The appearance of the work is well timed, coinciding with the large-scale effort toward better understanding and control of the cancer problem now being organized. The present volume should help in orientation of that effort by facilitating evaluation of the biochemical studies in this field.

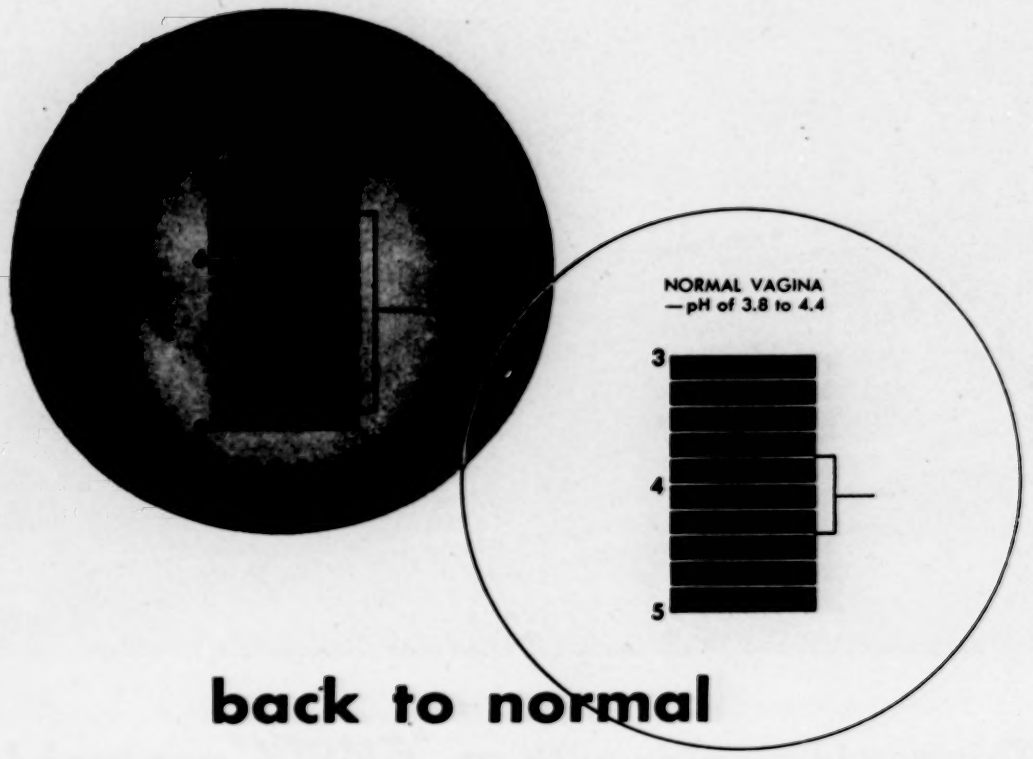
Following a brief introduction to the oncological sciences and a consideration of the general phenomena and taxonomy of cancer, the author considers the induction of tumors, attempts at control of tumor induction and growth, and the properties of tumors. The induction of tumors is discussed under the headings extrinsic factors (carcinogens) and intrinsic factors (sex hormones, mammary tumor inciter for mice, viruses). Attempts to control induction and growth of tumors are divided according to methods classifiable under nutrition, endocrinology and chemotherapy. The chemistry of tumors, a subject with which the author has been especially identified, and the chemistry of the tumor-bearing host comprise the main chapters of the section dealing with the properties of tumors. A frank and objective appraisal of the present status of experimental and clinical cancer research concludes the text.

Thirty-nine figures and 104 tables are interspersed throughout the book. Each chapter is followed by a list of selected references. An author and subject index complete the work.

Dr. Greenstein has summarized an impressive amount of data dealing with the biochemistry of cancer and the cancer-bearing subject, particularly in connection with experimental animal tumors and in such fields as carcinogenic agents, mammary tumorogenesis in mice, and comparative enzyme studies in normal and neoplastic tissues. Even more impressive, however, is the amount of properly orientated investigation which, as the author makes clear, is still needed, particularly in the biochemistry of human cancer. It is evident that what has been accomplished is merely an indication of the potentialities of the biochemical approach to the problem of cancer.

Dr. Greenstein remarks that "cancer research at the present time appears to be conducted along two diverging streams, one experimental and the other clinical, and neither is very much aware of what the other is doing." The present volume should prove an important step forward in correcting this situation.

A. B. G.

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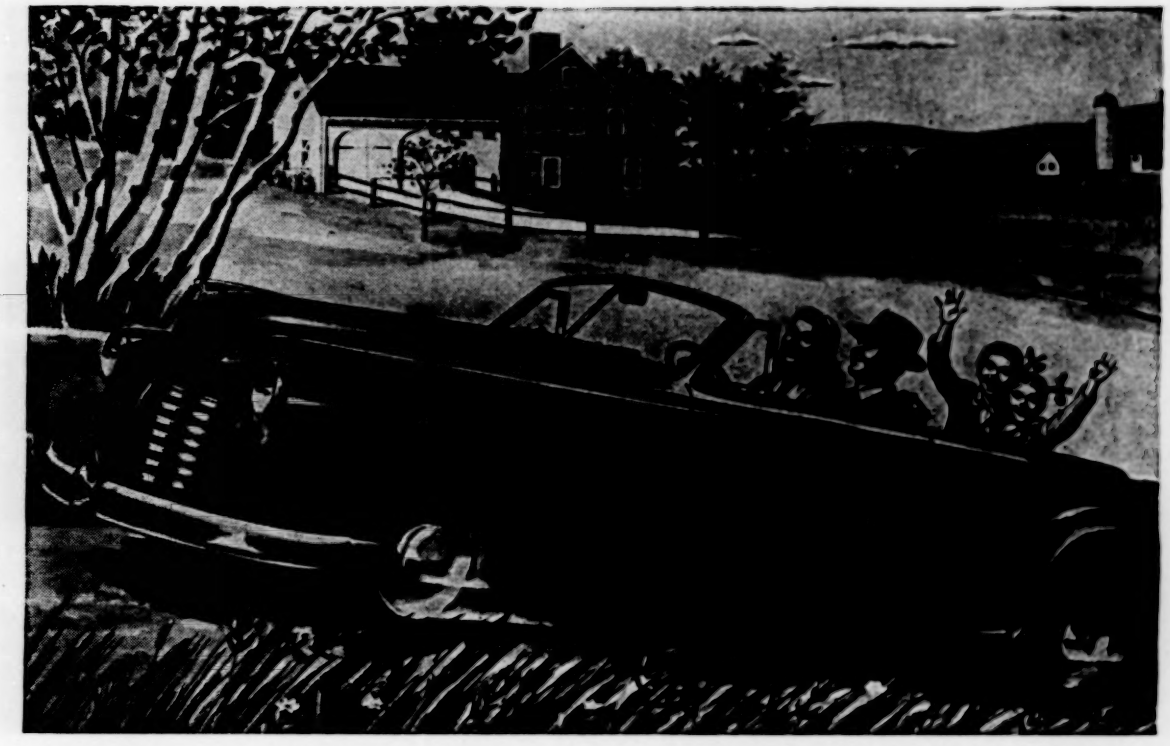
## SEARLE

RESEARCH IN THE SERVICE OF MEDICINE



# This car is running with an "EMPTY" gas tank!

EVEN AFTER the gas gauge says "empty" a modern car can keep going for a good many miles. Here's why.

Automobile manufacturers know human nature. They figure that, sooner or later, we'll get careless, or misjudge how far we have to go. So the gas gauge is set to show "empty," while there are still a couple of gallons left in the tank.

**This reserve supply** is a swell idea that has kept many a family from getting stuck.

It's an even better idea for a family's budget!

*A reserve supply of dollars* is a lifesaver in case of financial emergency. It will keep your family going if sudden illness strikes, or unexpected expenses show up.

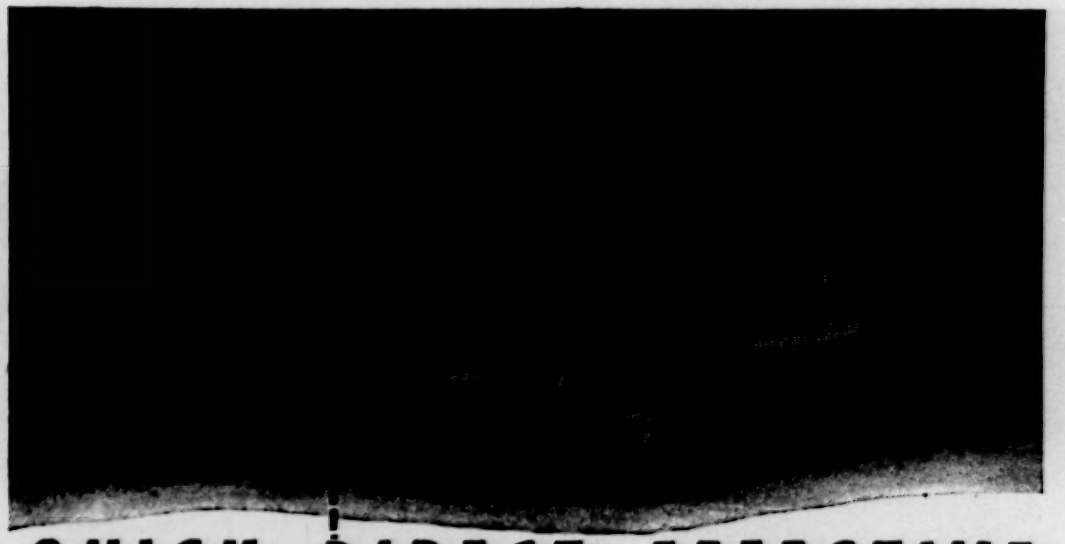
And one of the easiest ways to build just such a cash reserve is *buying U. S. Savings Bonds on the Payroll Savings Plan!*

**Millions of Americans** have discovered that *automatic* Bond buying is the quickest, surest way of saving money. What's more, the money you save in Bonds buckles right down and starts *making more money*—in just 10 years you get back $100 for every $75 you put in today.

**So keep on buying Bonds** on the Payroll Plan. Buy all the extra Bonds you can, at any bank or post office. And remember, you're helping your country as well as yourself—for every Bond you buy plays a part in keeping the U. S. strong and economically sound!

## Save the easy way..buy your bonds through payroll savings

*Contributed by this magazine in co-operation with the Magazine Publishers of America as a public service.*



# QUICK-DIRECT-EFFECTIVE

And so is FERRO-ARSEN. For most rapid hemoglobin regeneration and for increased probability of patient's response, Ferro-Arsen for 26 years has been satisfying thousands of physicians.

Ferro-Arsen represents controlled therapy in the management of hypochromic anemia. It places the iron directly in the blood stream where it is required and where it can be quickly effective.

**Ferro-Arsen is available in 5 cc and 10 cc ampuls.**

Ten cc ampuls contain as much iron and as much arsenic as do four grains of iron cacodylate. This may be compared with the one grain in ampuls of iron cacodylate known as Iron and Arsenic. Yet Ferro-Arsen is not irritating and its use has been singularly free from toxicity.

MADE FOR MEN OF SKILL BY SKILLED MEN

George A. Breon & Company

Pharmaceutical Chemists

KANSAS CITY 10, MISSOURI

NEW YORK · ATLANTA · LOS ANGELES · SEATTLE

**For the nutritionally deficient patient on a salt-free diet**

# Sodium-Free Protinal for protein therapy

With the advance of years, effective nitrogen balance through nutrition becomes increasingly difficult to maintain.

In such instances increased oral protein intake is necessary for the restoration and maintenance of a *positive nitrogen balance* in the aged. These intact protein-carbohydrate granules of Protinal are *sodium-free* and contain all the amino acids necessary to maintain life and growth. Where there is a normal functioning of the gastrointestinal tract, with protein deficiency, **PROTINAL** is indicated.

Gerontal patients will find sodium-free **PROTINAL** (Plain and Chocolate Flavor) pleasant tasting, readily digestible and highly effective. Twenty grams of **PROTINAL** with each meal are adequate in most cases where increased protein intake is necessary. Available in 8-ounce and 1-pound bottles.

## Protinal

a product of modern research

NATIONAL DRUG COMPANY

**THE NATIONAL DRUG COMPANY**
**PHILADELPHIA 44, PA.**

PHARMACEUTICALS, BIOLOGICALS, BIOCHEMICALS FOR THE MEDICAL PROFESSION

FOR EVERY OFFICE PROCEDURE

REQUIRING ANTISEPSIS

The indications for the use of an antiseptic in the physician's office are indeed many and varied . . . So much depends upon the efficacy of the antiseptic used that its selection becomes a matter of prime importance.

Phe-Mer-Nite (a brand of phenylmercuric nitrate) is a ***dependable*** antiseptic. It is bacteriostatic in dilutions as high as 1:1,000,000; it destroys spore-forming organisms in dilutions as high as 1:37,500; it is so nontoxic and nonirritating that it may be used in dilutions as low as 1:1000.

For routine use on the unbroken skin, Tincture Phe-Mer-Nite, 1:3000, is the antiseptic of choice. The tincture is intended primarily for preoperative skin preparation . . . For routine use in the treatment of abrasions, lacerations, infections, burns, and other skin lesions, Solution Phe-Mer-Nite, 1:1000, usually diluted further with four parts of water, is the antiseptic of choice. It is also used as a spray or gargle in infections of the nose and throat . . . The solution is effective even in the presence of blood, pus, or exudate. It is a dependable agent for the sterilization of instruments and rubber gloves.

Phe-Mer-Nite is a powerful bactericide—stable, odorless, nontoxic, nonirritating to the tissues—dependable in every procedure requiring antisepsis.

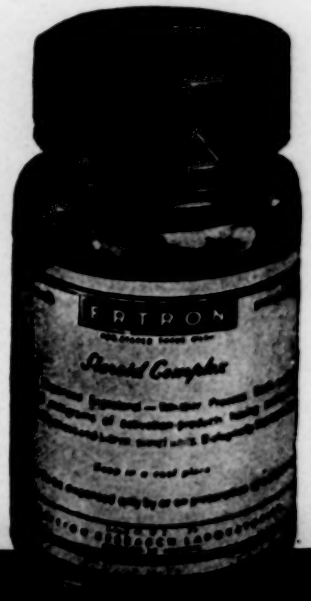
**The S. E. MASSENGILL COMPANY**
**Bristol, Tenn.-Va.**
NEW YORK • SAN FRANCISCO • KANSAS CITY

# SEVENTEEN PUBLISHED REPORTS

*May we remind you that there are 17 published reports in leading medical journals, dealing with the use of Ertron-Steroid Therapy in Arthritis? We shall gladly send reprints for your file.*

# ERTRON

**Steroid Complex**




NUTRITION RESEARCH LABORATORIES

CHICAGO

"BE NOT SICK TOO LATE,
NOR WELL TOO SOON."

POOR RICHARD'S ALMANAC (1734)

*BENJAMIN FRANKLIN*
*(1706-1790)*

**TODAY, THE DOCTOR SAYS IT THIS WAY:**

***"If you're not completely* well, *you're* sick."**

In nutrition, the value of such an attitude is well established. Today, vitamin deficiencies are properly recognized as diseases needing prompt and adequate treatment. To most physicians, adequate treatment includes *thorough* multivitamin therapy. To many physicians *thorough* multivitamin therapy means

*Thera-Vita*
Reg. U. S. Pat. Off.

**THERAPEUTIC VITAMIN CAPSULES**

***Each capsule contains:***

| | |
|---|---|
| Vitamin A (liver oil conc.) | 12,500 U.S.P. Units |
| Thiamine Hydrochloride ($B_1$) | 10 mg. |
| Riboflavin ($B_2$) | 10 mg. |
| Niacinamide | 100 mg. |
| Pyridoxine Hydrochloride ($B_6$) | 1 mg. |
| Calcium Pantothenate | 10 mg. |
| Ascorbic Acid (Vitamin C) | 150 mg. |
| Vitamin D (Activated Ergosterol) | 1,250 U.S.P. Units |

**DOSE:** 1 to 3 capsules daily as directed by physician.
**PACKAGING:** Bottles of 100 capsules.

OMNIS ORBIS
WARNER
ESTABLISHED 1856

*Thera-Vita* is a therapeutic multivitamin.
To prevent its indiscriminate use, PRESCRIBE IT.

**WILLIAM R. WARNER & CO., INC. • NEW YORK • ST. LOUIS**